The 38th Sapporo International Cancer Symposium

Integrated Cancer Analysis:
Science creates advanced diagnosis and therapies

Royton Sapporo
July 11 (Thu) -13 (Sat), 2019
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Cover photos:
• Landscape of Sapporo City
  (Odori Park Area)
• Statue of Dr. William S. Clark
  (Founder of Hokkaido Univ.)
Welcome Message

It is my great honor to welcome all of you to the 38th Sapporo International Cancer Symposium hosted by the Sapporo Cancer Seminar Foundation (SCSF). The annual symposium series was first organized in 1981 by SCSF, with strong desire to create a scientific platform where frontline cancer researchers can unreservedly discuss various scientific issues of cancer. Especially, this symposium is a precious opportunity for young researchers and doctors who are involved in cancer research to meet top Japanese and international scientists in Sapporo.

The title of this symposium in 2019 is "Integrated Cancer Analysis: Science Creates Advanced Diagnosis and Therapy", and we aim to proceed integrated understanding of cancer. The speed of applying new research findings to clinical diagnosis or treatment is accelerating, and it has been more difficult to completely separate basic and clinical research, thus the integrated cancer analysis is required. In fact, the emergence of next generation sequencer (NGS) has rapidly and dramatically changed cancer genome analysis with profound understanding of cancers, and companion diagnosis (coDx) and NGS-based clinical test has been established for determination of the molecular targeted drugs for treatment as personalized/precision medicine. Comprehensive analysis includes cancer signal transduction, clonal evolution, heterogeneity, cancer stem cells, and circulating tumor cells, genome and epigenome analysis by using advanced technology including artificial intelligence. I am very pleased with world-renowned researchers in these topics get together in Sapporo and discuss the current situation as well as major challenges and advancements.

In July, the city of Sapporo is blessed with greenery as well as beautiful colors of many plants and flowers. I hope that all of you will have fruitful discussion during the symposium and enjoy your stay in this beautiful city.

Shinya Tanaka, M.D., Ph.D.
Chair of the 38th Sapporo International Cancer Symposium
Professor
Department of Cancer Pathology, Faculty of Medicine
WPI-ICReDD (WPI-Institute for Chemical Reaction Design and Discovery),
GI-CoRE (Global Institute for Collaborative Research and Education)
Global Station of Soft Matter,
Hokkaido University, Japan
General Information

Date: July 11-13, 2019
Venue: Royton Sapporo
N1, W11, Chuo-ku, Sapporo 060-0001, Japan
TEL: +81-11-271-2711
Language: This symposium is held in English as the official language
Organizer: Sapporo Cancer Seminar Foundation (http://scsf.info/)

Chairpersons:
Chair: Shinya Tanaka (Hokkaido University, Japan)
co-Chair: Hirotoshi Akita (Hokkaido University, Japan)
co-Chair: Hisataka Sabe (Hokkaido University, Japan)
co-Chair: Kyoko Hida (Hokkaido University, Japan)

Program committee:
Raymond B. Birge (Cancer Institute of New Jersey, USA)
Lu-Hai Wang (China Medical University, Taiwan)
Wataru Yasui (Hiroshima University, Japan)
Michiyuki Matsuda (Kyoto University, Japan)
Masanobu Shindoh (Tenshi University, Japan)
Kyoko Hida (Hokkaido University, Japan)
Shingo Ichimiyia (Sapporo Medical University, Japan)
Mishie Tanino (Asahikawa Medical University, Japan)
Masahiro Sonoshita (Hokkaido University, Japan)

Banquet: will be held on Friday, July 12
Group photo: will be taken before the lunch on Saturday, July 13

Meeting Office:
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Presentation Guidelines

【Oral Presentation】

• Venue: Empress hall, Royton Sapporo Hotel 2F
• Presentation time:
  Special lectures: the speech is 35 - 40 min., followed by Discussion (total 45 min)
  Lectures: the speech is 25 min., followed by Discussion (total 30 min)
• Language:
  All speakers are requested to make their presentation material in English.
  This Symposium are presented and discussed in English.
• Audio-Visual Materials:
  1. Please bring your presentation data in USB memory device, or your own personal computer to PC operation desk in Empress hall at the latest 30 minutes before your presentation, and check whether all the data are shown properly. If you have prepared the presentation data on a Macintosh, or you wish to show a movie, you are requested to bring your own PC.
  2. When you are next one in line to give your presentation, please be seated on the Next Speakers Seat.

【Poster Presentation】

• Date and time: Friday, July 12, 16:45 - 18:00
• Venue: Regent hall, Royton Sapporo Hotel 2F

• Poster Panel: 90 cm (wide) x 200 cm (high)
• Mounting: Friday, July 12, 8:30 - 12:00
• Viewing: Friday, July 12, 12:00 - 16:45
• Removal: Friday, July 12, 18:00 - 21:00

1. Please prepare presentation material (poster) in English.
2. Poster Session will take place in a free-discussion style. Presenters are requested to be in front of the poster panels during discussion time (Friday, July 12, 16:45 - 18:00).
3. Any posters remaining on the panels after the removal time will be discarded by the secretariat.
1 Empress Hall
2 Regent Hall
4 Crystal Room A
8 Foyer
9 Elevators
10 Escalators
11 Cloak
Program

**July 11 (Thu)**
16:00-18:00  Registration for invited speakers and chairpersons
18:00-19:40  Welcome reception (Pearl Hall A・B, 20F)

**July 12 (Fri)**
(Empress Hall, 2F)
8:30-9:00  On-site registration
9:00-9:05  **Welcome address**, Organizing committee, Director, Prof. Masanori Hatakeyama
9:05-9:10  **Opening address**, Chairperson, Prof. Shinya Tanaka

**Session 1: Advanced investigation of cancer basics**
Chairpersons: Prof. Raymond B. Birge (Cancer Institute of New Jersey, USA)
                Prof. Michiyuki Matsuda (Kyoto Univ., Japan)

[S1-1] 9:10-9:40
Prof. Stephan M. Feller (Institute of Molecular Medicine, Germany)
**Intrinsically disordered signal integration platform proteins in cancer cells as novel targets?**

[S1-2] 9:40-10:10
Prof. Michiyuki Matsuda (Kyoto Univ., Japan)
**Roles of epidermal growth factor-family proteins in cell growth and collective cell migration of epithelial cells**

[S1-3] 10:10-10:40
Prof. Bruce Mayer (Univ. of Connecticut School of Medicine, USA)
**Integrating tyrosine phosphoproteomics and computational modeling in cancer**

10:40-10:55 Coffee break

[S1-4] 10:55-11:25
Prof. Masahiro Sonoshita (Hokkaido Univ., Japan)
**A whole animal platform for generating novel anti-cancer drugs**

[S1-5] 11:25-11:55
Prof. Lu-Hai Wang (China Medical Univ., Taiwan)
**Dysregulation of cystathionine γ-lyase promotes prostate cancer progression and metastasis**

11:55-13:00 Lunch (Regent Hall)
Tumor heterogeneity-related topics
13:00-13:45
Chairperson: Prof. Akitake Mukasa (Kumamoto Univ., Japan)
Prof. Do-Hyun Nam (Samsung Medical Center, South Korea)
Pharmacogenomic landscape of patient-derived tumor cells informs precision oncology therapy

Session 2: Microenvironment for cancer stem cells
Chairpersons: Prof. Stephan M. Feller (Institute of Molecular Medicine, Germany)
Associate Prof. Hidemitsu Kitamura (Hokkaido Univ., Japan)

[S2-1] 13:45-14:15
Prof. Marius Sudol (National Univ. of Singapore, Singapore)
The role of YAP oncogene in metastasis and mechano-medicine

[S2-2] 14:15-14:45
Prof. Shinya Tanaka (Hokkaido Univ., Japan)
Engineered hydrogels for rapid induction of cancer stem cells

14:45-15:00 Coffee break

[S2-3] 15:00-15:30
Prof. Lijun Liu (Northeastern Univ., China)
The cell cycle machinery in proliferation, pluripotency and differentiation of mammalian stem cells

[S2-4] 15:30-16:00
Prof. Kyoko Hida (Hokkaido Univ., Japan)
Abnormalities of tumor endothelial cells and cancer progression

Cancer stem cell-related topics
16:00-16:45
Chairperson: Prof. Toshihiko Torigoe (Sapporo Medical Univ., Japan)
Prof. Hideyuki Saya (Keio Univ., Japan)
Cancer stem cells: targets for cancer eradication

16:45-18:00 Poster presentation (Regent Hall)

18:00-20:00 Banquet (Regent Hall)
July 13 (Sat)
(Empress Hall, 2F)

Session 3: Novel therapeutic and diagnostic strategies for human cancers
Chairpersons: Prof. Lijun Liu (Northeastern Univ., China)
Senior Staff Scientist. Shinji Kohsaka (National Cancer Center Res. Institute, Japan)

[S3-1] 9:00-9:30
Prof. Anindyta Dutta (Univ. of Virginia, USA)
LncRNAs and germline SNPs for predicting outcome in gliomas

[S3-2] 9:30-10:00
Prof. Raymond B. Birge (Cancer Institute of New Jersey, USA)
Targeting phosphatidylserine and TAM receptors as a vulnerability in cancer

[S3-3] 10:00-10:30
Prof. Toshihiko Torigoe (Sapporo Medical Univ., Japan)
Novel immunodiagnostic and immunotherapeutic strategies targeting cancer stem cells

10:30-10:45 Coffee break

[S3-4] 10:45-11:15
Prof. Shumpei Ishikawa (The Univ. of Tokyo, Japan)
ImmunoGenomics of diffuse-type gastric carcinoma

[ Special lecture 3 ] Cancer genome-related topics
11:15-12:00
Chairperson: President Prof. Hirotohsi Akita (Hokkaido Univ. Hospital, Japan)

Prof. Hiroyuki Aburatani (The Univ. of Tokyo, Japan)
Wnt Signaling in Liver Cancer

12:00-12:15 Group photograph
12:15-13:20 Lunch

[ Special session for gastric cancer ]
13:20-14:20
Chairpersons: Prof. Wataru Yasui (Hiroshima Univ., Japan)
Prof. Bruce Mayer (Univ. of Connecticut Sch Med, USA)
13:20-13:50 (Basic)  
Prof. Masanori Hatakeyama (The Univ. of Tokyo, Japan)  
**Gastric carcinogenesis driven by the *Helicobacter pylori* CagA oncoprotein**

13:50-14:20 (Clinical)  
President Masahiro Asaka (Health Sciences Univ. of Hokkaido, Japan)  
**Effect of *Helicobacter pylori* eradication therapy on gastric cancer in Japan**

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**Session 4: Advanced pathological technology and diagnosis**  
Chairpersons: Prof. Beatrice Knudsen (Cedars-Sinai Medical Center, USA)  
Prof. Shumpei Ishikawa (The Univ. of Tokyo, Japan)

[S4-1] 14:20-14:50  
Prof. Beatrice Knudsen (Cedars-Sinai Medical Center, USA)  
**Machine learning and artificial intelligence (A.I.) in pathology: a novel approach to cancer analysis**

[S4-2] 14:50-15:20  
Prof. Masahiko Kuroda (Tokyo Medical Univ., Japan)  
**The practice of pathological diagnosis using AI**

15:20-15:30 Coffee break

[S4-3] 15:30-16:00  
Prof. Hiroshi Nishihara (Keio Univ., Japan)  
“PleSSision”; a pathologist edited multigene genomic test promotes cancer precision medicine in Japan

[S4-4] 16:00-16:30  
Senior Staff Scientist, Shinji Kohsaka (National Cancer Center Res. Institute, Japan)  
**Application of a high-throughput functional evaluation of variants of unknown significance to personalized medicine**

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**Conclusive and Perspective Talk**  
16:30-17:00  
Chairperson: Prof. Anindya Dutta (Univ. of Virginia, USA)

Prof. Hisataka Sabe (Hokkaido Univ., Japan)  
**Pancreatic KRAS/TP53 oncogenes promote immune evasion via activating eIF4A/4E-dependent translation and protein prenylation**

17:00-17:05 Closing remarks
Day 1

July 12 (Thu)

Empress Hall
Intrinsically disordered signal integration platform proteins in cancer cells as novel targets?

Stephan M. Feller
Charles Tanford Protein Research Center
Institute of Molecular Medicine
Tumor Biology Section
Martin Luther University Halle-Wittenberg, Halle, Germany

ABSTRACT
Nature has evolved several families of large intrinsically disordered proteins (IDPs) that serve as important hubs in cellular decision making (1-3). Examples include the GAB, IRS, BCAR1 and FRS family proteins. Fundamentally important biological processes like cell death, cell division and cell migration are decided in signaling protein complexes which are assembled upon such platform proteins. When deregulated, these complexes and processes can drive cancer development. In the case of GAB1 and GAB2, evidence for their aberrant functioning in various tumors is readily accumulating. The specific targeting of GAB-based signal processing complexes could thus become useful as a therapeutic strategy. Unfortunately, interfering with IDP functions through small molecule drugs is often not trivial, due to their great conformational plasticity. Nevertheless, IDPs sometimes transiently adopt secondary structure elements when binding to their specific signaling partners, which aids in defining important interacting regions and function-driving configurations and residues. Our biochemical and biophysical analyses of GAB1 and GAB2 have helped us to identify helical elements in the otherwise intrinsically disordered protein tails, which form upon partner protein binding, and to characterize their properties to near atomic resolution (4). These (PPII and 3-10) helices have been strictly conserved in evolution for hundreds of millions of years, pointing to their great significance.

We are currently starting to explore these epitopes for their suitability to generate inhibitory molecular mimics with in silico screening (5) and rational design approaches. In addition, GAB protein composite epitopes crucial for other signaling protein binding events are now being studied in our group by NMR and crystallography, potentially providing additional inroads for novel types of small molecule inhibitor tools and possibly even for designing new anti-cancer drugs.

References.
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EDUCATION/TRAINING
1981-1989 Biology studies (Diploma), Universities of Kaiserslautern & Heidelberg, Germany
1994 PhD in Cell Biology & Biochemistry, Rockefeller University, New York, NY, USA
2000 Habilitation in Molecular Oncology & Biochemistry, University of Würzburg, Germany

POSITIONS AND HONORS
1990-1994 Graduate student, Rockefeller University, New York, NY, USA
1994-1995 Postdoctoral Researcher, Rockefeller University
1995-2001 Junior Research Group Leader (Cell Signaling Group), Institute for Radiation & Cell Biology, University of Würzburg, Germany
2001-2013 Lecturer & Head of Research Group “Biological Systems Architecture”, Weatherall Institute of Molecular Medicine, Oxford University, United Kingdom
2013-Present Professor of Tumor Biology, Martin Luther University Halle-Wittenberg, Germany
2017-Present Deputy Director Charles Tanford Protein Research Center

SELECTED PUBLICATIONS
3. Paster, W et al. 2015, A THEMIS:SHP1 complex promotes T-cell survival. EMBO J 34, 393-409, 2015.
Roles of epidermal growth factor-family proteins in cell growth and collective cell migration of epithelial cells

Michiyuki Matsuda
Kyoto University, Kyoto, Japan

ABSTRACT

Epidermal growth factor (EGF)-family proteins are the major inputs to the Ras-ERK MAP kinase cascade. However, their roles still remain elusive in vivo. We have shown that ERK exhibits pulse-like activation in tissue culture cells and epithelial cells in a manner dependent on EGF receptor-family proteins. In epidermal basal layer cells, stochastic ERK activation in a few cells is propagated laterally up to ca. 50 µm in 30 min, which phenomenon was named stochastic propagation of radial ERK activity distribution (SPREAD). SPREAD is dependent on EGF receptor, suggesting that EGF-family proteins mediate cell-to-cell ERK activation. Similar stochastic ERK activation and propagation were also observed in the intestinal epithelium of living mice. Interestingly, we found that the basal ERK activity was maintained by ErbB2, whereas the stochastic ERK activation was dependent on EGF receptor, both of them contribute to efficient replication of intestinal epithelial cells. At the wound edge of epidermis, the ERK activation wavelets were superimposed to generate large parallel waves, which reached up to several hundred micrometres. We found that epithelial cells move against the direction of the ERK activation pulses. Optogenetic generation of ERK activation waves could induce cell migration against the direction of ERK activation pulse. Thus, EGF-family proteins, not only promotes cell growth, but also determine the direction of collective cell migration during wound healing.

References.
CONTACT INFORMATION
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EDUCATION/TRAINING
1977-1983 Faculty of Medicine, The University of Tokyo, Awarded the degree of M.D.
1983-1987 Department of Pathology, Graduate School of Medicine, The University of Tokyo, Awarded the degree of Ph.D. in Pathology for a thesis entitled "Origin of the medulloblastoma experimentally induced by human polyomavirus JC", Work supervised by Professor Kazuo Nagashima

POSITIONS AND HONORS
1987-1988 Researcher at Department of Pathology, National Institute of Health, Japan.
1988-1990 Postdoctoral associate at the Rockefeller University
1990-1996 Senior Researcher at Department of Pathology, National Institute of Infectious Diseases, Japan
1996-2000 Director, Department of Pathology, Research Institute, International Medical Center of Japan
2001-2006 Professor, Department of Tumor Virology, Research Institute for Microbial Diseases, Osaka University, Japan
2006-2017 Professor, Department of Pathology and Biology of Diseases, Graduate School of Medicine, Kyoto University
2007-2018 Professor, Laboratory of Bioimaging and Cell Signaling, Graduate School of Molecular and System Biology, Division of Systemic Life Science, Graduate School of Biostudies, Kyoto University
2017-2018 Council member, Science Council of Japan
2018-2019 Director, Research Center of Dynamic Living Systems, Graduate School of Biostudies, Kyoto University

1994 Sugiura Young Investigator Award from the Japanese Society for Virology.
1997 Young Investigator Award from the Japanese Cancer Association.
2008 Sagawa Cancer Research Grant Award
2011 Memorial Mochida Academic Award
2018 The Nakatani Award, Grand Prix.
2019 Japan Pathology Award

SELECTED PUBLICATIONS
Integrating tyrosine phosphoproteomics and computational modeling in cancer

Bruce J. Mayer
University of Connecticut School of Medicine
Farmington, USA

ABSTRACT

Tyrosine phosphorylation controls many of the cell behaviors that are deregulated in cancer, and the aberrant activity of tyrosine kinases is a frequent driver of tumorigenesis. Therefore the global state of tyrosine phosphorylation provides valuable information, which could be used to classify tumors and to predict clinical outcomes such as progression and response to targeted therapy. We have shown that SH2 profiling, a method we developed to quantify global phosphotyrosine (pTyr) patterns, can be used to stratify human cancers including chronic lymphocytic leukemia (CLL). SH2 profiling is based on quantification in a cell sample of the phosphorylated binding sites for the set of pTyr binding modules that are used by the cell to read and interpret changes in tyrosine phosphorylation during signaling. SH2 profiling does not, however, provide information on the identity of phosphorylated binding proteins, and this makes it challenging to understand the mechanistic basis for pTyr patterns that correlate with clinical outcomes. To address this issue, we are using the CLL system to develop a workflow for incorporating quantitative SH2 binding data into mechanistic computational models of B cell signaling. We are building detailed models using the Virtual Cell (VCell) and COPAS1 modeling frameworks, which incorporate the major species involved in signaling from the B cell receptor to key downstream outputs. The major phosphosites contributing to SH2 binding profiles that correlate with outcomes are being identified and incorporated into models. We will also use B cell and CLL cell lines and primary human CLL cells to measure quantitative signaling parameters and biological outputs under various experimental perturbations to calibrate the model and validate model predictions. By forging a link between global pTyr data, data-driven modeling, and mechanistic computational models of signaling networks, we will uncover the mechanistic basis for correlations between pTyr state and clinical outcomes for CLL. Such insights are likely to provide novel predictive markers and novel strategies for therapy for CLL. These studies will also serve as a springboard for similar studies in other malignancies.
CONTACT INFORMATION
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EDUCATION/TRAINING
1978-1982 Wesleyan University, BA in Biology
1984-1989 Rockefeller University, PhD in Viral Oncology
1989-1993 Postdoctoral Fellow, Whitehead Institute and Rockefeller University

POSITIONS AND HONORS
1993-1999 Assistant Investigator, Howard Hughes Medical Institute, Children's Hospital, Boston, MA
1993-2000 Assistant Professor, Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, MA
2000-2006 Associate Professor, Department of Genetics and Developmental Biology, University of Connecticut School of Medicine, Farmington, CT
2006-present Professor, Department of Genetics and Genome Sciences, University of Connecticut School of Medicine, Farmington, CT
2000 Raymond and Beverly Sackler endowment award

SELECTED PUBLICATIONS
A whole animal platform for generating novel anti-cancer drugs

Masahiro Sonoshita
Hokkaido University, Sapporo, Japan

ABSTRACT

Clinical kinase inhibitors are commonly used off-label for diseases for which they were not originally intended. Such drugs have demonstrated benefits for some patients but often at the cost of significant toxicity and dosing problems. Synthetic tailoring of approved drugs for new indications is often difficult, as the most appropriate targets may not be readily apparent and therefore few roadmaps exist to guide chemistry.

In this talk, I will present our novel platform for drug development by multidisciplinary approach for accessing novel target and chemical space starting from the FDA-approved class of kinase inhibitors. Employing chemical and genetic modifier screens in Drosophila, with computational modeling, we obtained a novel class of ‘tumor calibrated inhibitors’ with strongly improved therapeutic index against medullary thyroid carcinoma (1, 2). Application of this platform to a variety types of cancers will be also discussed.

References.
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EDUCATION/TRAINING
1995-1999 The University of Tokyo Faculty of Pharmaceutical Sciences, Tokyo, Japan
1999-2001 The University of Tokyo Graduate School of Pharmaceutical Sciences, Tokyo, Japan
2001-2004 Kyoto University Graduate School of Medicine, Kyoto, Japan

POSITIONS AND HONORS
2008-2010 Assistant Professor, Kyoto University Graduate School of Medicine, Kyoto, Japan
2010-2012 Senior Lecturer, Kyoto University Graduate School of Medicine, Kyoto, Japan
2012-2017 Associate Professor, Kyoto University Graduate School of Medicine, Kyoto, Japan
2013-2017 Visiting Researcher, Icahn School of Medicine at Mount Sinai, New York, USA
2017-2018 Postdoctoral Fellow, Icahn School of Medicine at Mount Sinai, New York, USA
2018-Present Professor, Hokkaido University Institute for Genetic Medicine, Sapporo, Japan

SELECTED PUBLICATION
Dysregulation of cystathionine $\gamma$-lyase promotes prostate cancer progression and metastasis

Lu-Hai Wang
China Medical University, Taichung, Taiwan

ABSTRACT

Hydrogen sulfide (H2S), an endogenous signaling gaseous molecule, is involved in various physiological activities, including vessel relaxation, regulation of cellular bioenergetics, inflammation, and angiogenesis. By using xenograft orthotopic implantation of prostate cancer PC3 cells and subsequently comparing bone metastatic- versus primary tumor-derived cancer cells, H2S-producing enzyme cystathionine $\gamma$-lyase (CTH) was upregulated in bone metastatic PC3 cells. CTH promoted NF-$\kappa$B nuclear translocation through H2S-mediated sulfhydration on cysteine-38 of NF-$\kappa$B p65 subunit, resulting in the increased IL-1$\beta$ expression and H2S-induced cell invasion. Knockdown of CTH resulted in significantly reduced IL-1$\beta$ expression and cell invasion in vitro, as well as reduced tumor growth, angiogenesis/lymphangiogenesis in the tumor microenvironment, and distant metastasis in an orthotopic implanted xenograft mouse model. Clinically, expression of CTH was elevated in late-stage prostate cancer patients, and higher CTH expression correlated with poor survival from TCGA prostate cancer RNA-seq datasets. Together, our findings provide evidence that CTH generated H2S promotes prostate cancer progression and metastasis through IL-1$\beta$/NF-$\kappa$B signaling pathways.
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EDUCATION/TRAINING
1966-1970 National Taiwan University. B.S. in Zoology.

POSITIONS AND HONORS
Positions:
2008-2017 Distinguished Investigator and Director, Division of Molecular and Genomic Medicine, National Health Research Institute, Taiwan
2012-2017 Chair Professor, Chiao Tung University, Taiwan
2011-2012 Joint Professor National Tsin Hua University, Taiwan
2011-2012 Adjunct professor National Taiwan University
2011 Sept-2012 Aug Acting vice president, National Health Research Institute
2012 Sept-Dec Acting President, National Health Research Institute
2012 Dec-2014 July Vice President, National Health Research Institute
2017-present Vice President & Chair Professor, China Medical University.

Honors:
2010 Academician, Academia Sinica, Taiwan
2010-2014 President, Chinese Association of Cell and Molecular Society
2012 Fellow, TWAS (The World Academy of Science
2013 Outstanding Breast Cancer Research Award, Breast Cancer Foundation, Taiwan

SELECTED PUBLICATIONS
Pharmacogenomic landscape of patient-derived tumor cells informs precision oncology therapy

Do-Hyun Nam

Director/Institute for Refractory Cancer Research, Samsung Medical Center
Professor/Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine
Professor/Department of Health Sciences & Technology, SAIHST, Sungkyunkwan University
Seoul, South Korea

ABSTRACT

The fundamental tenet of precision medicine involves genomic and molecular characterization of tumors to guide optimal therapeutic approach for individual patient. However, as most solid tumors harbor multiple genetic aberrations, predicting a successfully therapy based on genomic analysis alone remains challenging. An integrated approach consisting of genomic analysis of the patient tumor, in parallel with direct assessment of drug response on patient tumor derivatives is the next step towards precision medicine.

Towards this goal, we have established a big-data driven comprehensive study of genomic and transcriptomic profiles of 462 patient tumor-derived cells (PDCs) across 14 different cancer lineages, together with response to 60 targeted agents. Through our robust and multi-layered analytical approach, we provide unprecedented insights into dynamic pharmacogenomic associations, including molecular determinants that elicit therapeutic resistance, and potential repurposing target specific therapy. Collectively, our systematic approach provides a significant conceptual advance towards precision medicine treatment.
CONTACT INFORMATION
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EDUCATION/TRAINING
Professor Do-Hyun Nam graduated from Seoul National University College of Medicine in 1988 and received Ph.D. degree in Seoul National University College of Medicine. After obtaining medical degree, Professor Nam started his successful career as a clinical and research fellow at Department of Neurosurgery, Seoul National University Hospital and Samsung Biomedical Research Institute. He continued training for a career in cancer biology as a postdoctoral fellow at University Texas MD Anderson Cancer Center in Houston.

POSITIONS AND HONORS
During his prolific career in Samsung Medical Center (SMC), Professor Nam has held several prestigious appointments such as the Director of Division of Quality Assurance at the Clinical Trial Center and the Director of the Caner Stem Cell Research Center. Presently he has served as the Director of the Institute of Refractory Cancer Research (IRCR) at the SMC and the Professor of department of neurosurgery at the Sungkyunkwan University School of Medicine. Professor Nam has extensive experience and expertise in the field of brain tumor research. He has authored over 200 peer-reviewed articles and has received numerous awards for his scientific accomplishments.

SELECTED PUBLICATIONS
The role of YAP oncogene in metastasis and mechano-medicine

Marius Sudol

National University of Singapore, Singapore,
& Mount Sinai School of Medicine, New York, USA

ABSTRACT

YAP is a WW domain-containing protein that acts as a potent oncogene and stemness factor. It is one of the two main effectors of the Hippo tumor suppressor pathway. YAP is a transforming gene of the chromosome 11q22 amplicon, and its expression is elevated at high frequency in human cancers, including liver, breast, ovarian and stomach cancer. Our recent work showed that YAP regulates the acto-myosin network by suppressing Rho-GTPase via Rho-GTPase activating protein 29 (ARHGAP29) being a direct transcriptional target of YAP in human gastric cancer. We showed that YAP promoted the expression of ARHGAP29 to suppress the RhoA -LIMK-cofilin pathway, thereby destabilizing F-actin. The overexpression of YAP caused cytoskeletal rearrangement by altering the dynamics of F-actin/G-actin turnover, thus promoting migration. In a mouse model, circulating tumor cells (CTCs) exhibited an increase in ARHGAP29 RNA level compared with cells at primary tumor sites. Moreover, increased ARHGAP29 expression correlated with shortened survival of human gastric cancer patients. Importantly, we showed that ARHGAP29 is critical in regulating cancer metastasis in a mouse model of liver cancer metastasizing to lungs.

We have also identified YAP and TAZ specific transcripts and we are characterizing them now as mechano-responsive transcripts that regulate cell metastasis and mechano-sensing.

Cancer cells are generally softer than normal cells. By increasing the rigidity of cancer cells to the level of normal cells via novel therapeutic interventions, and by reducing rigidity of extracellular matrix of tumors we could provide a new modality to treat cancer in unison with other standard therapies.

References.
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EDUCATION/TRAINING
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Graduate Student Fellowship from Merinoff Cancer Fund (1982-1983)
Damon Runyon-Walter Winchell Cancer Fund Fellowship (1983-1985)
Junior Faculty Research Award from American Cancer Society (1987-1990)
FIRST NIH Grant Award from National Cancer Institute (1987-1992)
Klingenstein Award in the Neurosciences (1991-1994)
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Human Frontier Science Program Grant (1993-1996)
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Grant Award from Muscular Dystrophy Association (1995-2001)
NIH PPG on Gene Therapy (1997-2001)
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NIH RO1 on Dystrophin WW domain (2000-2003)
Human Frontier Science Program Grant (with Stan Fields); Second Award (2000-2003)
NIH PPG on Function of PKD1 Gene (2003-2008)
Tier 3 Grant on Morphogenesis and RTKs (with Mike Sheetz); (2017-2022)

SELECTED PUBLICATIONS
List of the most important publications from the Sudol laboratory, out of 175 in total:
Engineered hydrogels for rapid induction of cancer stem cells

Shinya Tanaka

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ABSTRACT
Polymer hydrogels as biomaterials to mimic microenvironment can be utilized to investigate cellular and biological reactions for applications in advanced medical care. In fact, double-network (DN) hydrogel composed of poly-(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) and poly-(N,N’-dimethyl acrylamide) (PDMAAm), is a soft and tough material (1) that resembles biological tissues and being used for cartilage regeneration (2,3). For complete cure of cancer patients, eradication of cancer stem cells (CSCs) is required. CSCs are resistant to chemo- and radiotherapies, and are a source of recurrence. However, detection of CSCs is extremely difficult, because cancer tissue includes only a few of them. Establishing an efficient method for identifying CSCs would ultimately enable the development of approaches to eradicate them. Here, we present a novel approach to generating CSCs with a DN gel, and thereby a model to investigate their properties. By placing six human cancer cells (KM G4, HeLa, A549, WiDr, J82, and Fuji) onto DN gels, cells rapidly formed clusters with spherical structures emerging within 24 hours that expressed stemness markers including Sox2, Oct3/4, and Nanog. Cells with highly tumourigenic properties similar to those of CSCs were observed after injecting SCID mice with a small number of DN gel-stimulated cancer cells. The DN gel altered the expression levels of tyrosine kinases (TKs), including EGFR, MET, Src, and FAK, with differential time courses. Microarray analysis revealed increased osteopontin (OPN), which has been previously shown to have an essential role in the induction and maintenance of cancer stemness. For application, DN gel could reveal the CSCs-specific expression of the TK receptor in patient-derived brain cancer cells, suggesting a possible eradication of CSCs by TK inhibitor. These results suggest that DN gels can rapidly modulate cellular gene expression and facilitate the reprogramming of differentiated cancer cells towards CSCs, in a process termed HARP (hydrogel-activated reprogramming). DN gels demonstrated the molecular mechanism of cancer cell reprogramming which has been unknown, and DN gel-induced rapid induction of CSCs should contribute to discovery of therapeutic reagents to eradicate them in the future.

References.
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2002 Incitement Award of the Japanese Cancer Association
2003 Incitement Award of the Japanese Society of Pathology

SELECTED PUBLICATIONS
The cell cycle machinery in proliferation, pluripotency and differentiation of mammalian stem cells

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ABSTRACT

Cyclins, cyclin-dependent kinases (CDKs) and other components of the core cell cycle machinery drive cell division. Growing evidence indicates that this machinery operates in a distinct fashion in some mammalian stem cell types, such as pluripotent embryonic stem (ES) cells and cancer stem cells. Here we generated mouse cells and tissues lacking all G1 cyclins (D-type and E-type cyclins), and showed that several cell types, such as ES cells, can proliferate without any G1 cyclins, but mouse embryonic fibroblasts (MEFs) cannot. However, following ablation of G1 cyclins, ES cells attenuated their pluripotent characteristics, with the majority of cells acquiring the trophectodermal cell fate. We established that G1 cyclins, together with their associated cyclin-dependent kinases (CDKs), phosphorylate and stabilize the core pluripotency factors Nanog, Sox2 and Oct4. Treatment of murine ES cells, patient-derived glioblastoma tumour-initiating cells, or triple-negative breast cancer cells with a CDK inhibitor strongly decreased Sox2 and Oct4 levels. Our findings suggest that CDK inhibition might represent an attractive therapeutic strategy by targeting glioblastoma tumour-initiating cells, which depend on Sox2 to maintain their tumorigenic potential.

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2016 Best Poster Prize Award, Joint Retreat, Dana Farber Cancer Institute, USA
2011 Outstanding Doctoral Dissertation Award, Peking University, China

SELECTED PUBLICATIONS

 equipos de investigación para el año 2001-2004, incluyendo proyectos de investigación en el campo de la biología del cáncer, y ha recibido varios premios y reconocimientos, como el Premio de la Sociedad Americana de Oncología en 2017. Los trabajos de investigación de Liu se han publicado en varias revistas científicas de renombre, como el Journal of Clinical Oncology y el Journal of Biological Chemistry. Ha colaborado con varios investigadores y ha recibido financiamiento de la National Institutes of Health y la American Society of Hematology.
Abnormalities of tumor endothelial cells and cancer progression

Kyoko Hida
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ABSTRACT

Tumor growth and metastasis are dependent on angiogenesis, which is the formation of new blood vessels. The balance between angiogenic stimulators and inhibitors regulates angiogenesis in the tumor microenvironment. Tumor blood vessels, especially the endothelial cells lining tumor blood vessels (tumor endothelial cells [TECs]), are important targets in cancer therapy. As newly formed tumor blood vessels originate from pre-existing normal vessels, tumor blood vessels and TECs have traditionally been considered to be the same as normal ones. However, tumor blood vessels have a distinctively abnormal phenotype, including morphological alterations. Recently, it has been revealed that TECs constitute a heterogeneous population, exhibiting characteristics that are induced by tumor microenvironmental factors. Furthermore, TECs contribute to cancer progression through metastasis. For example, TECs in highly metastatic tumors aberrantly express chemoattracting factor which stimulates cancer cell intravasation, in turn they instigate tumor cells to metastasize. Also, TEC intracellular adhesion molecule, VE-cadherin expression was downregulated by tumor-extracellular vesicles (EVs), causing in tumor metastasis. Besides, we have found that TECs express ABCB1, a drug transporter molecule and support cancer cells even during chemotherapy. Our experimental results have shown that targeting such abnormal TECs could show the anti-tumor effects in the mouse model. TEC abnormalities related to cancer progression will be to provide insight into new anticancer therapies.

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2018- Professor, Vascular Biology and Molecular Pathology, Graduate School of Dental Medicine, Hokkaido University
2010 The Japanese Society of Pathology Research Awards
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2018 The award in 11th Shiseido Female Researcher Science Grant

SELECTED PUBLICATIONS
Cancer stem cells: targets for cancer eradication

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ABSTRACT

Tumors comprise heterogeneous cell types, including cancer stem cells (CSCs), progenitor cells, and differentiated cells. Chemoresistance is a major issue in cancer therapy that be a potential cause of relapse and is a key characteristic of CSCs, but the development of novel therapeutic approaches for targeting these cells are limited. We found that expression of a CSC marker, CD44, in particular variant forms of CD44 (CD44v), contributes to the defense against reactive oxygen species (ROS) by promoting the synthesis of reduced glutathione (GSH), a primary intracellular antioxidant. CD44v interacts with and stabilizes xCT, a subunit of a glutamate-cystine transporter, and thereby promotes the uptake of cystine for GSH synthesis. Therefore, ablation of CD44 reduced GSH levels and increased ROS levels, leading to suppression of tumor growth and metastasis in both transgenic and xenograft tumor models. Based on these preclinical findings, we conducted clinical trials using an xCT inhibitor for cancer patients.

We previously established osteosarcoma-initiating (OSi) cells by introducing the gene for c-Myc into bone marrow stromal cells of Ink4a/Arf knockout mice. These OSi cells are composed of two distinct clones: highly tumorigenic cells (AX cells) similar to bipotent committed osteochondral progenitor cells, and tripotent cells of low tumorigenicity (AO cells) similar to mesenchymal stem cells. In contrast to AX cells, AO cells are highly resistant to conventional chemotherapeutic agents such as doxorubicin and thus identified as chemoresistant stemlike cells. We found that inhibition of Rho-kinase (ROCK) elicited terminal adipocyte differentiation in stemlike AO cells through negative regulation of the transcriptional coactivator megakaryoblastic leukemia 1 (MKL1) associated with actin depolymerization. We also found that the clinically administered ROCK inhibitor fasudil significantly suppressed the in vitro growth and in vivo tumorigenicity of stemlike AO cells and parental OSi cells. Our findings thus provide a new therapeutic strategy based on the induction of trans-terminal differentiation via modulation of actin cytoskeleton dynamics for therapy-resistant osteosarcoma stem cells.

References.
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2001 The Deborah M. Richman Memorial Lecture, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, USA
2008 The 6th Special Research Award, Sagawa Foundation for Promotion of Cancer Research, Japan
2008

SELECTED PUBLICATIONS
Day 2
July 13 (Sat)
Empress Hall
LncRNAs and germline SNPs for predicting outcome in gliomas

Anindya Dutta
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ABSTRACT

Diffuse low-grade and intermediate-grade gliomas (together known as lower grade gliomas, WHO grade II and III) develop in the supporting glial cells of brain and are the most common types of primary brain tumor. We have developed a computational model, UVA8, for prognosis of lower grade gliomas by combining long noncoding RNA (lncRNA) expression, Cox regression, and L1-LASSO penalization. The model was trained on a subset of patients in TCGA. Patients in TCGA, as well as a completely independent validation set (CGGA) could be dichotomized based on their risk score, a linear combination of the level of each prognostic lncRNA weighted by its multivariable Cox regression coefficient. UVA8 is an independent predictor of survival and outperforms standard epidemiological approaches and previous published lncRNA-based predictors as a survival model. Guilt-by-association studies of the lncRNAs in UVA8, all of which predict good outcome, suggest they have a role in suppressing interferon-stimulated response and epithelial to mesenchymal transition. The expression levels of eight lncRNAs can be combined to produce a prognostic tool applicable to diverse populations of glioma patients.

To ask how much specificity there is in the function of a prognostic lncRNA, we carried out structure-function studies on LINC00152/CYTOR, upregulated in GBMs and aggressive IDH1/2 wt grade II and III gliomas with the upregulation associated with poor patient outcomes. Inhibition of the mostly cytoplasmic LINC00152 decreases, and overexpression increases cellular invasion. PARIS and Riboseq data, together with secondary structure prediction, identifies a protein bound stem-loop at the 3' end of LINC00152 whose overexpression increases, and point mutation suppresses invasion of GBM cell lines. Thus, the structure-function studies suggest significant specificity in the oncogenic function of an lncRNA.

Although most of the focus in oncology has been on somatic mutations in the cancer, we wondered whether a Genome-Wide-Association-Study (GWAS) can identify germline variants predictive of survival in glioma patients. From a pool of over four million variants in The Cancer Genome Atlas whole exome sequencing and RNA sequencing datasets, we identified two germline variants that are predictive of poor patient outcomes by Cox regression, controlling for eleven (clinical and molecular) covariates currently in use for prognostication. rs61757955 is a germline variant found in the 3' UTR of GRB2 associated with increased KRAS signaling, CIC mutations, and 1p/19q co-deletion. rs34988193 is a germline variant found in the tumor suppressor geneANKDD1a that causes an amino acid change from a highly conserved lysine (on an ankyrin repeat loop) to glutamate. This variant was found to be predictive of poor prognosis in two independent lower grade glioma datasets. Thus GWAS with germline variants should be explored in parallel with somatic mutations for predicting the responsiveness of a cancer patient to therapy.
SELECTED PUBLICATIONS


7. ENCODE project consortium. The ENCODE pilot project: identification and analysis of functional elements in 1% of the human genome. *Nature* 447, 799-816, 2007. (Dutta’s group provided and analyzed the DNA replication data for the consortium.) (F1000 citation)


Targeting phosphatidylserine and TAM receptors as a vulnerability in cancer

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ABSTRACT

The physiological fate of cells that die by apoptosis is their rapid recognition and clearance by both non-professional and professional phagocytes (efferocytosis). Apoptotic cells, by externalizing phosphatidylserine (PS) from the internal to the external surface of the plasma membrane, act as potent negative regulators of immune responses, promoting immune-suppression and the resolution of inflammation under physiological conditions to maintain tissue tolerance. In contrast to the homeostatic function of efferocytosis under physiological conditions, tumors, in particular, exist in a chronic dynamic balance of proliferation, metabolic stress, and apoptosis that magnify the post-mortem immunosuppressive effects of apoptotic cells in the tumor microenvironment (TME). In turn, persistent apoptotic cells in the TME suppress host tumor immunity by engaging a series of PS receptors called TAM receptors (Tyro3, Axl, and Mertk). While TAMs are overexpressed in a vast array of tumor types, whereby the level of expression correlates with the tumor grade and the emergence of chemo and radio resistance to targeted therapeutics, they are also implicated as inhibitory receptors expressed on infiltrating myeloid-derived cells, where they act as “myeloid checkpoint inhibitors”. We have recently shown that TAMs can act as PS-sensing receptors not only to induce PS-mediated efferocytosis but also to upregulate the immune checkpoint inhibitory ligand PDL1 demonstrating the existing of a PS/PS-R (TAM-receptor)/PD-L1 axis that operates in the TME to drive immune escape. Finally, we will discuss the current molecular rationale that anti-PS, anti-TAM, and anti-PD-L1 based therapeutics may have therapeutic value as combinatorial checkpoint inhibitors in cancer immunotherapy.

References.
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SELECTED PUBLICATIONS
Novel immunodiagnostic and immunotherapeutic strategies targeting cancer stem cells

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ABSTRACT

Immunotherapy has become the fourth therapeutic modality for advanced cancer. However, only 20-30% of the patients responded to the immune checkpoint blockade monotherapy even in immune-sensitive lung cancer. We developed a novel immunohistological profiling method for cancer tissues, Immunohistogram, which could visualize the disorders of cancer-immunity cycle in each cancer tissue. Comparison of the Immunohistogram between DNA mismatch repair (MMR)-deficient cancer and MMR-proficient cancer would be demonstrated. Cancer immunoprofiling using Immunohistogram would become a potent diagnostic tool for selection of therapeutic options and contribute to personalized precision medicine.

One of the barriers to be crossed in cancer therapy and prevention is a black box of cancer stem cells (CSCs). It is a central theme in cancer immunotherapy to reveal immunopathogenic properties of CSCs. We have successfully identified some tumor-specific antigens that were expressed in various CSCs and have important roles in tumorigenic capacity. We termed them functioning cancer stem antigens (fCSAs). Interestingly, one of the fCSAs was derived from an olfactory receptor family gene and another was from a long non-coding RNA. Specific T-cell responses were induced against these fCSAs and exerted superior tumor suppressive activity in vivo as well as cytotoxicity against CSCs in vitro. CSCs expressed some immunoinhibitory molecules such as PD-L1 and TGF-β. Based on these findings, we propose a novel immunotherapeutic and immunoprophylactic strategy targeting CSCs.
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SELECTED PUBLICATIONS
Immunogenomics of diffuse-type gastric carcinoma

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ABSTRACT

Diffuse-type gastric cancer (DGC) is a major subtype of stomach cancer and has unique biological and clinical features such as single cell infiltration, strong fibrotic stroma, and the possibility of massive metastasis / dissemination. Global genomic analysis so far has revealed the heterogeneity of gastric cancer genome and its immune microenvironment, as well as DGC’s unique characters. Cell composition estimation from large-scale transcriptomic data indicate that DGC is suggested to be classified as "immunologically cold tumor", and its poor responsiveness to immune checkpoint inhibitors has recently been validated in clinical trials. Based on the observation that B cell infiltration is relatively increased in DGC, we tried to delineate the details of immune composition of DGCs and did comprehensive profiling of T cell and B cell immune repertoires in clinical gastric cancer tissues. It revealed different patterns of response of T cell and B cell repertoire in the cancer environment, and frequent clonal expansion of tumor specific-B cells. The complementarity determining regions (CDRs) of immunoglobulins are substantially variable, and it was difficult to simply find common features of cancer specific immunoglobulin sequences. We then did deep neural network approach and successfully extract complex features of tumor specific immunoglobulins, which can also be used to classify cancer- or non-cancer status. In order to determine what antigens were recognized by the tumor specific dominant clones, we reconstructed human IgG antibodies from their RNA sequences, and found while many of the examined clones recognize self-antigens that have also been reported in autoimmune diseases, some clones recognize sulfated glycosaminoglycans (s-GAG), an unique subgroup of carbohydrates. Our analysis has shown that s-GAG is the major humoral cancer antigen in DGC, as the most dominant tumor infiltrating B-cell clones recognize s-GAG in approximately 30-40% of cases. These clones were successfully incorporated into cancer cells and induced cell death using antibody-drug conjugate technology.

These results uncover the unique immunogenic character of DGC, and give us the possibility of new therapy concept by modulating the humoral cancer immune system against this refractory cancer.

References.
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SELECTED PUBLICATIONS
Wnt Signaling in Liver Cancer

Hiroyuki Aburatani
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ABSTRACT

In the international cancer genome project over the last decade, 25,000 cancer genome data have been deposited to public databases, where we have contributed in the study of liver and stomach cancers. In early hepatocellular carcinoma (HCC), CTNNB1 and TP53 are most frequently mutated, mostly in a mutually exclusive manner, ranked next to TERT promoter. β-catenin protein is localized in nucleus in the advanced tumors with CTNNB1 mutation, while localized at plasma membrane in early HCCs.

Long noncoding RNAs (lncRNAs) have been found to be involved in cell growth and apoptosis, in part through epigenetic regulation. Wnt signal, which is frequently activated in various cancers, induces the expression of genes that regulate cell cycle and proliferation. While many genes have been identified as the targets of β-catenin, it is not fully understood how activated β-catenin regulates its downstream targets. We identified a β-catenin-target IncRNA, Inc12R, by combination of RNA-seq and ChIP-seq for β-catenin and histone modification. Lnc12R is overexpressed also in colorectal tumors with APC mutation in TCGA dataset. Knockout of Inc12R using CRISPR/Cas9 inhibits tumorigenesis in vivo. Repression of Inc12R resulted in H3K27 deacetylation and repressed β-catenin target genes, such as LGR5, without affecting the binding of β-catenin on their promoter. Finally, I will present the genomic profile of hepatoblastoma and discuss difference from hepatocellular carcinoma.

References.
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SELECTED PUBLICATIONS
ABSTRACT

With 723,000 deaths in 2012, gastric cancer is the third leading cause of cancer-related deaths worldwide. This malignancy is quite common in East Asian countries such as Japan, China and Korea; more than half of the world’s gastric cancer cases arise from this geographic area. Chronic infection with Helicobacter pylori, especially the cagA-positive strain, is causally associated with the development of gastric cancer. The cagA-encoded CagA protein, having a molecular weight ranging between 120~145-kDa due to the C-terminal sequence polymorphisms, is delivered into host gastric epithelial cells via type IV secretion. Once delivered, the bacterial protein aberrantly interacts with host proteins via its intrinsically disordered C-terminal tail, which contains two distinct protein-binding motifs, the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif and the CagA multimerization (CM) motif. Upon tyrosine phosphorylation by Src family kinases, the EPIYA motif acquires the ability to interact with and thereby deregulates SH2 domain-containing host proteins, particularly the pro-oncogenic phosphatase SHP2 that promotes mitogenesis while stimulating cell motility. CagA also binds to the polarity-regulating serine/threonine kinase PAR1b via the CM sequence and thereby inhibits the kinase activity, causing junctional and polarity defects. The magnitude for the pathobiological action of individual CagA has been linked to the qualitative (sequence) and quantitative (repeat number) polymorphisms in these protein-binding motifs. Recent crystal analysis has shed light on the structural basis determining the magnitude for the pathogenic action of the individual CagA species, which explains the high incidence of gastric cancer in East Asian countries.

Despite its importance in the development of gastric cancer, however, CagA is no longer required for the maintenance of gastric cancer cells once established. Thus elucidation of the role of CagA during neoplastic transformation provides an excellent opportunity to understand molecular mechanisms that promote the "Hit-and-Run" carcinogenesis, in which oncogenic CagA actions needs to be successively taken over by genetic and/or epigenetic alterations compiled in cancer-precursor cells during H. pylori infection. We will discuss a possible molecular mechanism underpinning CagA-directed "Hit-and-Run" carcinogenesis.
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1995-1999 Member and Chief, Department of Viral Oncology, Cancer Institute, Japanese Foundation for Cancer Research (GANKEI), Tokyo, Japan
1999-2000 Professor, Institute of Immunological Sciences, Osaka University, Osaka, Japan
2009-present Professor, Institute for Genetic Medicine, Hokkaido University, Sapporo, Japan

SELECTED PUBLICATIONS
Effect of Helicobacter pylori eradication therapy on gastric cancer in Japan

Masahiro Asaka
Health Sciences University of Hokkaido, Sapporo, Japan

ABSTRACT

In Japan, there have been approximately 50,000 deaths from gastric cancer annually for over 40 years with little variation. It has been reported that most gastric cancers in Japan are caused by Helicobacter pylori infection. H. pylori eradication therapy was approved for patients with chronic gastritis by the Japanese national health insurance scheme in February 2013 for patients with an endoscopic diagnosis of chronic gastritis is positive for H. pylori. We examined the effect on gastric cancer death rate 4 years after expansion of health insurance coverage. We conducted an epidemiological study and analyzed trends in prescription for H. pylori eradication therapy. We used the electronic medical claims database from Hokkaido, Japan to evaluate the impact of expansion of national health insurance coverage for H. pylori eradication therapy on deaths from gastric cancer. Data on deaths from gastric cancer were obtained from the Japanese Ministry of Health, Labour and Welfare and the Cancer Statistics in Japan (2015). Analysis of electronic claims records was performed using the National Database, mainly focusing on Hokkaido. Prescriptions for H. pylori eradication therapy and the number of patients treated for gastric cancer were also extracted from the Hokkaido database. Approximately 1.5 million prescriptions for H. pylori eradication therapy were written annually. Gastric cancer deaths fell each year: 48,427 in 2013, 47,903 in 2014, 46,659 in 2015, and 45,509 in 2016, showing a significant decrease after expansion of insurance coverage for H. pylori eradication therapy (P < 0.0001).

Prescriptions for H. pylori eradication therapy increased markedly after approval of the gastritis indication by the national health insurance scheme and was associated with a significant decrease in gastric cancer deaths.
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EDUCATION / TRAINING
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POSITIONS
1994-2011 Professor, Department of Gastroenterology, Hokkaido University Graduate School of Medicine,
2007-2010 Director, Hokkaido University Hospital
2011-2016 Professor, Department of Cancer Preventive Medicine, Hokkaido University Graduate School of Medicine
2016- President, Health Sciences University of Hokkaido

AWARDS WINNER
2009 Princess Takamatsu Cancer Research Fund Prizes
2011 Asahi Cancer Grand Prize
2011 Japan Medical Association Medical Award

SELECTED PUBLICATIONS

SCS2019 The 38th Sapporo International Cancer Symposium
Integrated Cancer Analysis: Science creates advanced diagnosis and therapies
Machine learning and artificial intelligence (A.I.) in pathology: a novel approach to cancer analysis

Beatrice S. Knudsen

Cedars-Sinai Medical Center, Los Angeles, California, USA

ABSTRACT

Pathologists diagnose cancer and determine cancer grade and severity through systematic evaluation of microscopic images. They have established a range of features in hematoxylin and eosin stained tissues that are indicative of malignant transformation. These features of tissue architecture are based on the organization of specific cell types, the growth patterns of glands and on nuclear and subnuclear morphology. During the last decade, computing power has increased to a point that computers can identify patterns of many features simultaneously in microscopic images. This is accomplished through training of convolutional neural networks, an integral building block of A.I. algorithms for digital image analysis. By quantifying the expression of histologic patterns, computers generate data for diagnosis, prognosis and integration with other OMICs data. We will present the use of A.I. algorithms for (1) prostate cancer prognostication in prostate needle biopsies, (2) quantification of neuroendocrine differentiation, which is involved in lethal prostate cancer progression and (3) quantification of chromosomal instability. In these use cases of pathology A.I., morphometric data are integrated with data from RNA sequencing to improve patient outcomes prediction and provide insight into the underlying mechanisms that link gene expression and prostate cancer morphology.
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EDUCATION/TRAINING
1982 – 1988 M.D.-Ph.D. training program, Cornell University Graduate School of Medical Sciences
1989 – 1990 Internship in Medicine, New York Hospital
1990 – 1995 Post-doctoral Fellowship, Rockefeller University
1995 – 1998 Anatomic Pathology Residency, New York Hospital

POSITIONS AND HONORS
Positions:
1998 – 2002 Assistant Professor of Pathology, Weill Medical College of Cornell University, New York, New York
1998 – 2002 Assistant Attending Pathologist, New York Presbyterian Hospital
2002 – 2008 Assistant Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington
2008 – 2011 Associate Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
2009 – 2011 Member, Molecular and Cellular Biology Graduate School Program, University of Washington
2011 – present Director of Translational Pathology
Professor of Biomedical Sciences and Pathology & Laboratory Medicine
Cedars-Sinai Medical Center, Los Angeles
2011 – 2016 Director of Biobank, Cedars-Sinai Medical Center, Los Angeles
2016 – 2018 Scientific Director of Translational Research Core

Affiliate Positions:
1996 – 1998 Visiting Scientist Rockefeller University
2004 – 2009 Affiliate Assistant Professor, Department of Pathology, University of Washington
2009 – 2011 Affiliate Associate Professor, Department of Pathology, University of Washington
2019 – present Adjunct Professor, Department of Biomedical Informatics, University of Stony Brook, NY

Honors:
1986 Julian Rachele Prize for paper publication
1987 Duvigneau Prize for oral paper presentation
1990 Revison Fellowship
2011 Prostate Cancer Foundation Creativity Award
2017 Prostate Cancer Foundation Impact Award

SELECTED PUBLICATIONS
The practice of pathological diagnosis using AI

Masahiko Kuroda
Tokyo Medical University, Tokyo, Japan

ABSTRACT

Recent studies of molecular biology have provided great advances for diagnostic molecular pathology. Traditional histological diagnosis is, however, still the most powerful method for diagnosis of diseases. We have mostly focused on digital pathology since 2003 collaborating with NEC. Then we have developed a novel computerized analysis system of gastric cancer (named as e-Pathologist), that allows rapid, automated histological analysis of H&E stained sections using SVM (Support Vector Machine) in 2013. On the other hand, DL (Deep Learning) method has been developed in recent years. While the SVM inputs feature quantities of pathological images measured in advance, the DL itself finds these feature quantities. Therefore, there is a possibility that AI can find feature quantities that are difficult to quantify by pathologist. The use of AI in pathology has just begun. The morphological image of the pathology contains a lot of information. By analyzing information from pathological images by AI, it is expected to be applied not only to pathology diagnostics but also to the field of cell biology. This time, I would like to discuss the current situation and problems in using AI in various pathological diagnoses.

References.
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1993-1996 The University of Tokyo, Faculty of Medicine
1996-1999 Postdoctoral research fellow at Skirball Institute, New York University

POSITIONS AND HONORS
1993-1996 Lecturer at Department of Pathology, Faculty of Medicine, The University of Tokyo
1999-2009 Assistant Professor at Department of Pathology, Tokyo Medical University
2009-Present Professor and Chair, Department of Molecular Pathology, Tokyo Medical University
2014-2018 Associate vice president, Tokyo Medical University

SELECTED PUBLICATIONS
"PleSSision"; a pathologist edited multigene genomic test promotes cancer precision medicine in Japan

Hiroshi Nishihara
Keio University, Tokyo, Japan

ABSTRACT
Development of genomic medicine enables us to perform contemporary clinical sequencing, while the acquisition of high quality biospecimen and the appropriate handling of these materials are indispensable. In Japan, several types of multigene genomic testing for cancer have been launched as a clinical examination since around 2016. We herein developed a novel cancer clinical sequencing system by amplicon exome sequence targeting 160 cancer genes; PleSSision (Pathologists edited, Mitsubishi Space Software supervised clinical sequence system for personalized medicine) collaborating with Mitsubishi Space Software Co. Ltd (MSS). In our system, genomic DNA was extracted from both tumor FFPE (formalin-fixed paraffin embedded) tissue and peripheral blood mononuclear cells as a normal control. The quality of extracted DNA was evaluated by TapeStation 2000 (Agilent) and the library made with GeneRead Comprehensive Cancer Panel (QIAGEN) was deeply sequenced using MiSeq. FastQ files were analyzed by MSS using original bioinformatics pipeline within 3 business days, and we identified cancer-specific somatic gene alteration such as SNV, Ins/Del and CNV. Finally, cancer board conference consisting of medical oncologists, pathologists, clinical laboratory technologists, bioinformaticians and clinical geneticists proposes the personalized treatment strategies based on the gene profiles. For 30 months, we examined 334 solid cancer patients and perform targeted exome sequence. As a result, the success rate of sequence was 98%, and detection rate of actionable gene mutation was 92%. In addition, 26 out of 205 (13 %) patients underwent “Genotype-matched treatment” based on our sequence report, and response rate (CR + PR) and disease control rate (CR + PR + SD) are 38% and 73%, respectively. In addition, we have recently launched “PleSSision-Exome”; whole exome sequence for cancer covering around 20000 genes. In this innovative system, we established high volume and deep clinical sequence for cancer tissue with reasonable cost as laboratory examination. We believe that our novel clinical sequencing system will vigorously promote cancer individualized medicine throughout Japan.

References.
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Mar, 2002 – July, 2004  Molecular pharmacology at University of California, San Diego, Department of Pharmacology, La Jolla, CA, USA

POSITIONS AND HONORS
2000 – 2008  Assistant Professor at Hokkaido University. “Signal Transduction in Cancer”
2008 – 2015  Associate Professor at Hokkaido University. “Molecular cancer pathology”
2015 – 2017  Professor at Hokkaido University. “Cancer Precision Medicine”
2017 – 2017  Division Manager at Hokkaido Cancer Center. “Cancer Precision Medicine”
2017 – present  Professor at Keio University. “Cancer Genomics and Precision Medicine”

SELECTED PUBLICATIONS
1. Omori, Y., ... , Nishihara, H., (16th), ... , Tanaka, S. Pathways of Progression From Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features. Gastroenterology 156, 647-661, 2019.
Application of a High-throughput Functional Evaluation of Variants of Unknown Significance to Personalized Medicine

Shinji Kohsaka
National Cancer Center Research Institute, Tokyo, Japan

ABSTRACT

The advent of next-generation sequencing technology has enabled to identify numerous somatic mutations across a variety of cancers, but many of the mutations are still variants of unknown significance (VUS) that await further investigation of clinical relevance. Here we present a mixed all nominated mutants in one (MANO) method to evaluate the transforming potential and drug sensitivity of VUS of oncogenes, and applied this method to 101 non-synonymous EGFR mutations and 55 non-synonymous ERBB2 mutations in a high-throughput manner. We discovered several novel activating mutations which probably drive tumorigenesis. Furthermore, EGFR and ERBB2 mutations showed varying drug sensitivities to tyrosine kinase inhibitors (TKIs). Our data thus supported the importance of examining uncommon mutations within EGFR and ERBB2, and also of functional evaluation of such mutations. MANO method may become a novel foundation for in vitro and in vivo assessments of variants of cancer-related genes to deliver precision medicine to individual cancer patients.
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2012-2014 Fellow, Memorial Sloan-Kettering Cancer Center, NY
2015-2017 Assistant professor, Graduate School of Medicine, The University of Tokyo
2017-Present Senior Staff Scientist, National Cancer Center Research Institute.
2013 Incitement Award of the Japanese Association for Molecular Target Therapy of Cancer
2018 Incitement Award of the Japanese Cancer Association
2019 The Young Scientists’ Prize of the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
2019 Incitement Award of the Japanese Association of Medical Science

SELECTED PUBLICATIONS
Conclusive and Perspective Talk

Pancreatic KRAS/TP53 oncogenes promote immune evasion via activating eIF4A/4E-dependent translation and protein prenylation

Hisataka Sabe
Hokkaido University, Sapporo, Japan

ABSTRACT

Although mutant KRAS and TP53 are the major oncogenes driving both the oncogenesis and malignancy of pancreatic ductal adenocarcinomas (PDACs), whether these oncogenes are also associated with cancer immune evasion remains to be determined.

We have demonstrated previously that the overexpression and increased signaling from ARF6 and its effector, AMAP1, are at the core of driving the invasion, metastasis, and treatment-resistance of different cancers, including breast cancer, renal cancer and lung cancer. Here we show that ARF6-AMAP1 pathway is the major target of KRAS/TP53 oncogenes to promote immune evasion of PDACs. Mutant KRAS promoted eIF4A/4E-dependent mRNA translation, culminating in enhanced ARF6 and AMAP1 expression. Platelet-derived growth factor (PDGF) is the major risk factor of PDAC. Mutant TP53 promoted ARF6 activation by PDGF, via previously reported mechanisms of enhanced expression of mevalonate pathway (MVP) enzymes and PDGF receptorβ. Consistently, the mouse model of human PDAC, namely KPC cells (LSL-Kras(G12D/+); LSL-Trp53(R172H/+); Pdx-1-Cre), express ARF6 and AMAP1 at high levels and use them for invasion and metastasis. Using the animal model, we demonstrated that the ARF6-AMAP1 pathway is closely associated with cancer immune evasion in vivo. Mechanistically, this pathway, as well as KRAS/TP53 oncogenes, eIF4A, eIF4E, mTORC1 and MVP, promoted PD-L1 dynamics and other aspects of immune evasion. Our results provide a set of molecular targets, which when blocked may each effectively kill PDACs by suppressing immune evasive phenotypes.
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EDUCATION/TRAINING
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PROFESSION
July 1986 Assistant Professor, Kyoto University School of Medicine
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Sept 1993 A ssistant Professor, Rockefeller University, Lab. of Molecular Oncology
April 1994 A ssociate Professor, Kyoto University Institute for Virus Research
April 1999 Head, Osaka Bioscience Institute Dept. of Molecular Biology
April 1999 Visiting Professor, Kyoto University Graduate School of Life Sciences
July 2009 Professor, Hokkaido University Graduate School of Medicine

AWARDS
1985 Special Research Fellow of the Japan Society for the Promotion of Science
1991 Human Frontier Science Program Organization Fellowship
1995 Grant from Mitsubishi Natural Science Foundation Grant
2010 Grant from Mitsubishi Natural Science Foundation Grant

SELECTED PUBLICATIONS
Posters

Poster Discussion: July 12 (Fri) 16:45 – 18:00
Regent Hall
Poster Presentations

[P-01] Futoshi Suizu (Div. of Cancer Biology, Institute for Genetic Medicine, Hokkaido Univ.)
A Novel Detection Systems of phosphatidylinositol 3-phosphate (PtdIns3P) for Molecular Imaging

[P-02] Kenta Terai (Graduate School of Biostudies, Kyoto Univ.)
Development of FRET biosensors comprised of longer wavelength fluorescence proteins

[P-03] Masamichi Imajo (Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido Univ.)
Alterations of ERK activity dynamics underlying tumor-specific traits in the intestinal epithelium

[P-04] Chitose Oneyama (Div. of Cancer Cell Regulation, Aichi Cancer Center Research Institute)
Src in endosomal membranes promotes exosome secretion and tumor progression

[P-05] Satoko Uemura (Dept. of Gastroenterological SurgeryII., Graduate school of Med, Hokkaido Univ.)
Role for signaling adaptor protein Crk in pancreatic cancer

[P-06] Keisuke Kuromiya (Div. of Molecular Oncology, Institute for Genetic Medicine, Hokkaido Univ. Graduate school of Chemical Sciences and Engineering)
Investigation of the role of AHNAK2 in cell competition

[P-07] Koki Kohashi (Div. of Molecular Oncology, Institute for Genetic Medicine, Graduate school of Chemical Science and engineering, Hokkaido Univ.)
Sequential oncogenic mutations affect the cell fate of RasV12 cells: from loser to winner in cell competition

[P-08] Kei Kozawa (Div. of Molecular Oncology, Institute for Genetic Medicine, Hokkaido Univ.)
The role of membrane protein X in carcinogenesis

[P-09] Takumi Konno (Dept. of Cell Science, Research Institute for Frontier Medicine, School of Medicine, Sapporo Medical Univ.)
Loss of ASPP2 promotes cell invasion and migration via LSR and YAP in human endometrial cancer
Significance of estrogen/GPR30 signaling and claudin-1 in cervical adenocarcinoma

Enhancer reprogramming for alveolar soft part sarcoma development

UHRF1 depletion and HDAC inhibition synergistically reactivate epigenetically silenced genes in colorectal cancer cells

p53 excludes EZH2 from H3.1 interactome during S phase to maintain histone code

Development of a new combinational epigenetic therapy of multiple myeloma

Deep sequencing uncovered initial and fate-determining mutations in well-differentiated neoplasias of the stomach

Artificial intelligence predicts the genetic information of the integrated diagnosis of brain tumors

The expression of Wnt5a on tumor cell membrane is associated with favorable pathological features and prognosis in hepatocellular carcinoma

Identification of gene sets inferring the survival of lung adenocarcinoma

Integrated therapeutic strategy for lethal tumors
Hiroshi Kitajima (Dept. of Molecular Biology, School of Medicine, Sapporo Medical Univ.)
Identification and functional analysis of a long noncoding RNA associated with chronic gastritis and gastric cancer

Chie Sato (Dept. of Molecular Diagnostic Pathology, School of Medicine, Iwate Medical Univ.)
Analysis of expression patterns of microRNAs in ovarian high-grade serous carcinoma

Yukitomo Ishi (Dept. of Neurosurgery, Hokkaido Univ. School of Medicine)
H3K27M mutation and prognosis in spinal cord gliomas

Takeshi Mikami (Dept. of Neurosurgery, Sapporo Medical Univ.)
Intracranial vasculopathy after radiation therapy for malignant tumors

Ayaka Sasagawa (Dept. of neurosurgery, Sapporo Medical Univ.)
Stroke mimics and chameleons caused, or characterized, by glioma

Shoichi Ukai (Dept. of Molecular Pathology, Graduate School of Biomedical and Health Sciences, Hiroshima Univ.)
Generation and functional analysis of 5-FU resistant gastric cancer organoids

Yusuke Ohta (Dept. of Pathology, Faculty of Medicine and Graduate School of Medicine, Hokkaido Univ.)
New micro-cell culture platform “micro/nanoplate” induces self-organization of microtumor in PDACs

Jun Suzuka (Dept. of Cancer pathology, Faculty of Medicine, Hokkaido Univ.)
Novel drug-screening system using hydrogel-induced cancer stem cells

Hirokazu Sugino (Dept. of Cancer Pathology, Faculty of Medicine, Hokkaido Univ.)
Induction of cancer stem cell properties through mechanosensitive ion channels

Satoshi Tanikawa (Dept. of Cancer Pathology, Faculty of Medicine, Hokkaido Univ.)
Development of the cryogel for neuronal tissue engineering
[P-30]  
Masahiro Sonoshita (Div. of Biomedical Oncology, Institute for Genetic Medicine, Hokkaido Univ.)  
**A whole-animal platform for developing novel anti-cancer drug leads**

[P-31]  
Nako Maishi (Dept. of Vascular Biology and Molecular Pathology, Graduate School of Dental Medicine, Hokkaido Univ.)  
**Increased ABCB1 expression in tumor blood vessels of urothelial carcinoma after chemotherapy**

[P-32]  
Dorcas Akuba-Muhyia Annan (Dept. of Vascular Biology and Molecular Pathology, Graduate School of Dental Medicine, Hokkaido Univ.)  
**Carbonic anhydrase 2 (CAII) is essential for tumor endothelial cell proliferation under various metabolic conditions**

[P-33]  
Akiteru Goto (Dept. of Cellular and Organ Pathology, Akita Univ., Graduate School of Medicine)  
**Macrophage-mediated transfer of cancer-derived components to stromal cells in gastric cancer**

[P-34]  
Takashi Akutagawa (Saga Univ.)  
**Cancer-adipose tissue interaction with fluid flow modulate cell kinetics and chemosensitivity in gastric cancer**

[P-35]  
Ken Imaizumi (Dept. of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido Univ.)  
**Alteration of the immunosuppressive population after neoadjuvant therapies for locally advanced rectal cancer**

[P-36]  
Umma Habiba (Dept. of Cancer pathology, Graduate School of Dental Medicine, Hokkaido Univ.)  
**Synergistic cytotoxicity of oncolytic adenovirus in combination with cisplatin chemotherapy**

[P-37]  
Yasuo Kokai (Dept. of Biomedical Engineering, Research Institute of Frontier Medicine, School of Medicine, Sapporo Medical Univ.)  
**CCL8 deficiency in host strongly inhibits early mortality of acute graft-versus-host disease in mice**

[P-38]  
Muhammad Baghdadi (Div. of Immunology, Institute for Genetic Medicine, Hokkaido Univ.)  
**A role for IL-34 in multiple myeloma-induced osteolytic disease**
Nanumi Han (Div. of Immunology, Institute for Genetic Medicine, Hokkaido Univ.)
Inhibition of IL-34 production by JQ1 as a novel therapeutic strategy in cancer therapy

Takuto Kobayashi (Div. of Immunology, Institute for Genetic Medicine, Hokkaido Univ.)
The impact of IL-34 on immunotherapy resistance in colorectal cancer

Naoki Hama (Div. of Immunobiology, Institute for Genetic Medicine, Hokkaido Univ.)
The potential involvement of Interleukin-34 in metastasis of ovarian cancer

Xiangdong Wang (Div. of Functional Immunology, Institute for Genetic Medicine, Hokkaido Univ.)
Arginase-1 is related to the malignancy of colon cancer cells

Huihui Xiang (Div. of Functional Immunology, Institute for Genetic Medicine, Hokkaido Univ.)
Neuropeptide signaling through NK2R is related to malignancy of colon cancer cells

Naoki Okada (Dept. of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido Univ.)
Inhibition of diacylglycerol kinase alpha activates anti-tumor effector T cells in tumor-bearing host

Tomoyo Shinkawa (Dept. of Pathology, Sapporo Medical Univ.)
Structural changes in peptide-HLA class I complexes predict neoantigen immunogenicity

Daisuke Kamimura (Div. of Molecular Psychoimmunology, Institute for Genetic Medicine, Hokkaido Univ.)
The inflammation amplifier promotes tumor progression in a mouse model

Haruka Wada (Div. of Immunobiology, Institute for Genetic Medicine, Hokkaido Univ.)
Tumor-initiating cell induce immuno-hyporesponsiveness following cellular senescence to macrophages guarantee its tumorigenesis

Masumi Tsuda (Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido Univ.)
WPI-Chemical Reaction Design and Discovery (ICReDD) develops highly efficient chemical reactions and the innovative products for all of humanity
[P-01]

A Novel Detection Systems of phosphatidylinositol 3-phosphate (PtdIns3P) for Molecular Imaging

Futoshi Suizu, Noriyuki Hirata, Thoria Donia, Bala Jyoti, Satoko Ishigaki, and Masayuki Noguchi

Div. of Cancer Biology, Institute for Genetic Medicine, Hokkaido Univ.

Phosphatidylinositol (PtdIns) plays a pivotal role in wide varieties of signal transduction pathway and/or membrane trafficking as a second messenger after binding to protein receptor in the cells. Seven possible different PtdIns (theoretically eight) are known to be present in mammalian cells by the different combination of phosphorylation of the D-position of the inositol ring. However, technology is limited partly due to the availability of the antibody which recognize individual specific PtdIns in mammalian cells. Currently, several PtdIns specific binding modules, such as GFP-fused FYVE (Fab-1, YGL023, Vps27, and EEA) domain, -PH (pleckstrin homology) domain or -PX domain, were often utilized for probing intracellular PtdIns in particular molecular imaging techniques. However, due to complexity of the GFP-fused technology, application is limited for the detection of intracellular specific PtdIns. We searched a small molecule which specifically recognize PtdIns3P, which is known to play an important role for regulation of autophagy activity. We identified an RNA aptamer which specifically recognizes PtdIns3P by means of SELEX (Systematic Evolution of Ligands by EXponential enrichment) technology from random RNA library as a possible novel molecular imaging tool. RNA aptamer will allow to overcome current limitation for the molecular probing system of PtdIns by GFP-fused PtdIns binding modules and/or antibodies. The RNA aptamer based molecular imaging technology will have a promise for dissecting the locus of the intracellular PtdIns, a critical second messenger of varieties of signal transduction in mammalian cells.

Keywords: phosphatidylinositol 3-phosphate, RNA Aptamer, Autophagy

[P-02]

Development of FRET biosensors comprised of longer wavelength fluorescence proteins

Tetsuya Watabe1, Kenta Terai2, Michiyuki Matsuda1,2

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2 Laboratory of Bioimaging and Cell Signaling, Graduate School of Biostudies, Kyoto Univ.

Genetically-encoded biosensors based on the principle of Förster(D+Srster resonance energy transfer (FRET) have been developed for the visualization of signaling molecule activities. Currently, most of them are comprised of cyan and yellow fluorescent proteins (CFP and YFP), precluding the use of multiple FRET biosensors within a single cell. Moreover, the FRET biosensors based on CFP and YFP are also incompatible with many optogenetic tools that can be stimulated as blue to green light. In order to overcome these problems, here we have developed FRET biosensors comprised of longer wavelength fluorescent proteins.

The FRET biosensors were designed to include a substrate peptide for protein kinase A (PKA), an FHA1 pThr-binding domain, a flexible linker, a red FP, and a far-red FP. We have extensively compared the order of the domains, the length of the linker, and the combination of red and far-red FPs. Consequently, we developed a FRET biosensor named OF-PKA biosensor, of which performance was comparable to that of AKAR3EV, a previously developed FRET biosensor comprising of CFP and YFP.

For the proof of concept, we first show monitoring of the PKA activity that was modulated by bPAC, an optogenetic generator of cyclic AMP. Under the condition of monitoring PKA activity by the OF-PKA biosensor, bPAC was not stimulated to the detectable level. Second, simultaneous monitoring of activities of two protein kinases were achieved with OF-PKA and FRET biosensors based on CFP and YFP. Thus, the new FRET biosensors with red and far-red FPs will provide versatile tools for cell biology.

Keywords: FRET Imaging, Optogenetics, PKA
Alterations of ERK activity dynamics underlying tumor-specific traits in the intestinal epithelium

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Acting downstream of many growth factors, extracellular signal-regulated kinase (ERK) plays a pivotal role in regulating a variety of biological processes including cell proliferation, survival, and differentiation. Since ERK activation promotes proliferation of many types of cells, its deregulated/constitutive activation is among general mechanisms for cancer. Recent advances in bioimaging techniques have enabled to visualize ERK activity in real-time at the single-cell level. In this study, by using transgenic mice expressing a highly sensitive biosensor for ERK activity, we uncovered the ERK activity dynamics in intestinal epithelial cells (IECs) and their association with tumor characteristics. Intravital imaging identified two distinct modes of ERK activity, sustained and pulse-like activity, in IECs. The sustained ERK activity was mediated by ErbB2 signaling, whereas the pulse-like activity was generated by EGFR signaling. Notably, deregulated activation of Wnt signaling, the earliest event in intestinal tumorigenesis, augmented EGFR signaling and increased the frequency of ERK activity pulses through controlling expression of EGFR and its regulators, rendering IECs sensitive to EGFR inhibition. Furthermore, the increased pulse frequency was responsible for accelerated proliferation of tumor cells. These results show that ERK activity dynamics are defined by composite inputs from EGFR and ErbB2 signaling in IECs and alteration of their functional balance might underlie tumor-specific sensitivity to pharmacological inhibition of EGFR signaling.

Keywords: intestinal tumorigenesis, ERK MAP kinase, bioimaging, EGFR, ErbB2

Src in endosomal membranes promotes exosome secretion and tumor progression

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c-Src is a membrane-associated tyrosine kinase that has key roles in the signaling transduction that controls cell growth, adhesion, and migration. In the early stage of carcinogenesis, c-Src is activated under the plasma membrane and transduces oncogenic signals. Here we show that c-Src localized to the endosomal membrane has unique functions in c-Src–transformed cells. Our results indicate that activated c-Src in the endosomal membrane promoted the secretion of exosomes, in which c-Src was encapsulated. In addition, the ESCRT-interacting molecule, Alix was identified as a c-Src–interacting protein in exosomes. We revealed that the interaction between the SH3 domain of c-Src and the proline-rich region of Alix activates ESCRT–mediated intra-luminal vesicle (ILV) formation, resulting in the upregulation of exosome secretion in c-Src–transformed cells. We observed also a correlation between malignant phenotypes and Alix–dependent aberrant exosome secretion in Src–upregulated cancer cells. Collectively, our findings provide a unique mechanism for the upregulation of exosomes in cancer cells, as well as new insights into the significance of exosome secretion in cancer progression.

Keywords: Src, exosomes, endosome, tumor progression
**[P-05]**

**Role for signaling adaptor protein Crk in pancreatic cancer**

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**[Background]** While various chemotherapies do not produce sufficient effects in pancreatic cancer, new molecular targeted therapeutic agents are in great demand. Although KRAS mutations are frequently found in pancreatic cancer, we focused on the signaling adapter protein Crk (CT10-regulated kinase), which is involved in the downstream of various tyrosine kinases besides the RAS mutation. Crk, originally isolated as an oncogene fusion product of an avian sarcoma CT10 retrovirus, links tyrosine kinases and guanine nucleotide exchange factors (GEFs) such as C3G and Dock180 to activate small G-proteins Rap and Rac, respectively. Previous studies have shown that Crk controls cell proliferation, motility, adhesion, invasion, and metastasis of various human cancers including synovial sarcoma, ovarian cancer, breast cancer, and glioblastoma. This study aimed to elucidate the role of Crk in pancreatic cancer.

**[Materials and Methods]** Three human pancreatic cancer cell lines (PANC-1, AsPC-1, MIAPaCa-2) were used. For examination to confirm the expression of Crk, the degree of phosphorylation levels of related proteins were analyzed by immunoblotting. Crk knockdown cells were established using Crk-shRNA and phenotypic analysis was performed using various assays in vitro. A mouse orthotopic xenograft model was created as an in vivo experiment to evaluate survival rate.

**[Results]** Crk knockdown pancreatic cancer cells exhibited decreased phosphorylation of c-Met, and also cell proliferation, invasion, adhesion, and increased survival rate in orthotopic xenograft model.

**[Conclusion]** Crk is considered to be involved in c-Met related signal and in malignancy of pancreatic cancer.

Keywords: Crk, pancreatic cancer, molecular targeted therapy

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**[P-06]**

**Investigation of the role of AHNAK2 in cell competition**

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At the initial stage of carcinogenesis, a single mutation occurs in a cell within a normal epithelial layer. We have previously shown that RasV12-transformed cells are apically extruded from the epithelium when surrounded by normal cells, a process termed epithelial defense against cancer (EDAC). However, the molecular mechanisms underlying this phenomenon remain elusive. Here, using stable isotope labeling by amino acids in cell culture (SILAC)-based quantitative mass spectrometry for phosphorylated peptides, we have identified proteins that are specifically phosphorylated in the mix culture conditions of normal and RasV12-transformed cells compared to their single culture conditions. Among the identified phospho-proteins, we have focused on AHNAK2 as one of the largest-ratio-change proteins. We find that phosphorylation of AHNAK2 is upregulated in normal cells mixed with RasV12-transformed cells compared to that in normal cells cultured alone. In addition, AHNAK2-knockdown in normal cells suppresses apical extrusion. These data indicate that AHNAK2 is a crucial regulator of cell competition. Recently, we find that Ca²⁺-dependent Protein Kinase C regulates the phosphorylation of AHNAK2. Then, when we performed time-lapse imaging by using MDCK cells expressing GCaMP, the calmodulin-based Ca²⁺ sensor probe, we find that Ca²⁺ occurs more frequently in normal cells mixed RasV12-transformed cells compared to normal cells cultured alone. Furthermore, we identify that TRPC1 (Transient Receptor Potential channel 1), a stretch-activated Ca²⁺ channel, regulates the elevation of Ca²⁺ in normal cells mixed RasV12-transformed cells. Moreover, TRPC1 also regulates the phosphorylation of AHNAK2. Thus, we identify the TRPC1-Ca²⁺-AHNAK2 pathway, which converts mechanical forces into chemical reactions in cell competition. We would like to reveal the detail molecular mechanism in future studies.

Keywords: cell competition, phospho-SILAC, AHNAK2, Ca²⁺, TRPC1
Sequential oncogenic mutations affect the cell fate of RasV12 cells: from loser to winner in cell competition

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Recent studies have revealed that newly emerging transformed cells are often eliminated from epithelial tissues via cell competition with the surrounding normal epithelial cells. For example, when RasV12 cells are surrounded by normal cells, RasV12 cells are apically extruded from the epithelial layer. However, Ras mutations have been detected in various types of human cancer. During cancer development, sequential mutations occur in normal epithelia where double-transformed cells would expand their territory while being surrounded by single-transformed cells. Thus, we examine whether sequential oncogenic mutations can influence cell competition.

When RasV12 is induced in a mosaic manner within the Scribble-knockdown epithelia, apical extrusion is substantially suppressed, while the formation of protrusions is promoted. Then, Scribble-knockdown/RasV12 double mutant cells induce apoptosis of the surrounding Scribble-knockdown cells and actively engulf them. These results suggest that the fate of RasV12 cells is altered under Scribble-knockdown background. Moreover, the phagocytic maker CD68 is upregulated in Scribble-knockdown/RasV12 double mutant cells surrounded by Scribble-knockdown cells. Furthermore, inhibition of RhoA or Rho-kinase suppresses engulfment of the surrounding Scribble-knockdown cells. In addition, inhibition of the mTOR pathway suppresses apoptosis, engulfment of the surrounding Scribble-knockdown cells and CD68 expression of Scribble-knockdown/RasV12 double mutant cells. These results suggest that Rho pathway and mTOR pathway are upstream targets of engulfment.

We will clarify the upstream target of apoptosis and engulfment to elucidate the molecular mechanism further. We will also conduct analysis of in vivo experiment.

Keywords: Cell competition, Sequential oncogenic mutations, Engulfment, Cell death, CD68

The role of membrane protein X in carcinogenesis

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At the initial stage of carcinogenesis, a single mutation occurs in a cell within normal epithelia. However, at present, this precancerous condition is not a therapeutic target. The aim of this study is to detect mutated and/or precancerous cells at the initial stage of cancer. To this end, using the phage-antibody display screening, we attempt to identify surface molecules of which expression is upregulated in transformed cells.

From the screening, we have obtained 6000 - 7000 phage clones that specifically bind to RasV12-transformed cells but not to normal cells. Using antibodies generated from phage clones, we performed immunoprecipitation. As a result, we identified membrane protein X which is enhanced by RasV12 expression. In addition, we find that not only RasV12 but also c-Src or ErbB2 enhances expression of X. Furthermore, X expression is profoundly elevated in multi-layered structures. And knockout of X attenuates multi-layered structures of RasV12 cells. These data indicate that membrane protein X is a crucial regulator of the formation of multi-layered structures during carcinogenesis.

The formation of multi-layered epithelia occurs at the early stage of carcinogenesis. Therefore, we investigate the involvement of X in carcinogenesis. Using KPC mice (LSL-KrasG12D/+; LSL-Trp53R172H/+; Pdx-1-Cre), a mouse model for pancreatic cancer, we examine expression of X in epithelia at the early stage of cancer. As a result, high expression of X is observed in multi-layered structures of precancerous lesions. Furthermore, at the early stage of human breast cancer, expression of X is increased in multi-layered structures of precancerous breast epithelia. These data suggest that membrane protein X might be a target molecule for precancerous lesions of transformed epithelia.

However, it still remains unclear how membrane protein X is involved in the formation of multi-layered structures. This study would lead to establishment of novel biomarkers and/or new therapeutic applications for cancer prevention.

Keywords: Phage-antibody display screening, Multi-layered structures
Loss of ASPP2 promotes cell invasion and migration via LSR and YAP in human endometrial cancer

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Apoptosis-stimulating p53 protein 2 (ASPP2) is an apoptosis inducer that acts via binding with p53 and epithelial polarity molecule PAR3. In endometrial cancer tissues, downregulation of ASPP2 is observed and contributes to migration and invasion of cancer cells. However, the mechanisms remain unclear. Lipolysis-stimulated lipoprotein receptor (LSR) is a unique molecule of tricellular contacts of normal and cancer cells. We previously reported that the loss of LSR promoted cell invasion and migration via upregulation of TEAD1/AREG dependent on Yes-associated protein (YAP) in human endometrial cancer cells. In the present study, we investigated how the loss of ASPP2 induced cell migration and invasion in human endometrial cancer cell line Sawano in which high expressed ASPP2.

The loss of ASPP2 by the siRNA promoted cell migration and invasion. siRNA-YAP prevented the cell migration and invasion induced by siRNA-ASPP2. The loss of ASPP2 by the siRNA induced expression of phospho-YAP, claudin-1 and claudin-7 as well as that of LSR. Treatment with the antibody against c-terminal of ASPP2 downregulated ASPP2 at the membranes and upregulated expression of pYAP and claudin-1. The ASPP2 antibody induced cell migration and invasion via YAP. In conclusion, loss of ASPP2 promoted cell invasion and migration via LSR and YAP in human endometrial cancer cells. ASPP2 may play a crucial role in preventing malignancy of cancer cells together with LSR.

Keywords: ASPP2, LSR, YAP, tricellular tight junctions, malignancy

Significance of estrogen/GPR30 signaling and claudin-1 in cervical adenocarcinoma

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The incidence of uterine cervical adenocarcinoma has been increasing worldwide, especially in young women, and its prognosis is worse than that of squamous cell carcinoma (SCC) at the same stage and with the same tumor size. The main reasons for the worse prognosis are a higher rate of metastases and resistance to radiotherapy and chemotherapy. Therefore, a new treatment strategy is needed to improve the outcome of cervical adenocarcinoma. In the uterine cervix, non-neoplastic columnar epithelial cells are positive for classical estrogen receptors (ERs), whereas their expression is almost absent in adenocarcinomas. Furthermore, several studies demonstrated that classical ER expression was not associated with the prognosis or clinicopathological parameters of uterine cervical cancers. Therefore, cervical adenocarcinomas have been believed to be estrogen-insensitive neoplasms, and estrogen signaling has not been considered in the context of cervical adenocarcinomas. However, we unexpectedly found that cervical adenocarcinoma cells respond to a physiological concentration of estrogen. Here, we demonstrate that a membrane-bound type estrogen receptor, G protein-coupled estrogen receptor 30 (GPR30/GPER1), but not classical ERs, is highly expressed in cervical adenocarcinoma and mediates estrogen signaling. Estrogen/GPR30 signaling upregulated claudin-1, a cell surface molecule highly expressed in cervical adenocarcinomas, via ERK and/or Akt signaling. Knockout of claudin-1 induced apoptosis and significantly inhibited proliferation, migration and invasion of cervical adenocarcinoma cells and tumorigenicity in vivo. In surgical specimens, there was a positive correlation between claudin-1 expression and GPR30 expression. Double high expression of claudin-1 and GPR30 predicts poor prognosis in patients with cervical adenocarcinomas. The discovery of estrogen sensitivity is important because aberrant estrogen signaling may contribute to the development of cervical adenocarcinoma, and a high concentration of circulating estrogen may become its risk factor. Our findings indicate the possibility of a new therapeutic strategy targeting cell surface molecules GPR30 and claudin-1 in cervical adenocarcinomas.

Keywords: GPR30; claudin-1, cervical adenocarcinoma, estrogen, therapeutic target
Enhancer reprogramming for alveolar soft part sarcoma development

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Alveolar soft part sarcoma (ASPS) is a highly metastatic AYA generation neoplasm with ASPL-TFE3 (AT3) as the causative mutation. TFE3 belongs to MIT/TFE family (TFE3, TFEB, TFEC, MITF) genes that encode bHLH-LZ transcription factors bound to a common DNA consensus motif. We have recently exhibited that expression of TFE3 and TFEB C-termini could induce ASPS when they were fused to ASPL whereas no such an activity was observed for TFEC and MITF, suggesting TFE3/TFEB-specific oncogenic potencies for the ASPS cell-of-origin. ChIP-seq analyses of human and mouse ASPS cells showed frequent overlapping of AT3, histone H3K27ac and H3K4me3 DNA-binding at target loci, indicating frequent binding of AT3 to active enhancers. Many of the active enhancers are associated with canonical MIT/TFE target genes involved in the autophagy, lysosome/endosome and vesicle/protein transport pathways. Moreover, search for ASPS-specific targets associated with super-enhancers is undertaken. Taken together, our study will reveal uncharacterized mechanisms of oncogenic MIT/TFE transcription factors and mechanisms of ASPS development.

Keywords: ASPL-TFE3, Alveolar soft part sarcoma, fusion gene, reprogramming, MIT/TFE family

UHRF1 depletion and HDAC inhibition synergistically reactivate epigenetically silenced genes in colorectal cancer cells

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Hiromu Suzuki


UHRF1 is a major regulator of epigenetic mechanisms and is overexpressed in human malignancies. In this study, we examined the role of UHRF1 in colorectal cancer (CRC) epigenome. Transient UHRF1 knockdown rapidly induced genome-wide DNA demethylation in CRC cells. Infinium BeadChip assays and bisulphite pyrosequencing analyses revealed significant demethylation across entire genomic regions, including CpG islands, gene bodies, intergenic regions and repetitive elements. Nonetheless, UHRF1 depletion only minimally reversed CpG island hypermethylation-associated gene silencing. However, the combination of UHRF depletion and histone deacetylase (HDAC) inhibition synergistically reactivated the silenced genes and strongly suppressed CRC cell proliferation. UHRF1 depletion plus HDAC inhibition induced marked changes in gene expression profiles in CRC cells. Our results suggest that (i) maintenance of DNA methylation in CRC cells is highly dependent on UHRF1; (ii) UHRF1 depletion rapidly induces DNA demethylation, though it is insufficient to fully reactivate the silenced genes; and (iii) dual targeting of UHRF1 and HDAC may be an effective new therapeutic strategy.

Keywords: colorectal cancer, DNA methylation
p53 excludes EZH2 from H3.1 interactome during S phase to maintain histone code

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During DNA replication, parental histones are segregated into newly replicated chromatin, along with incorporation of new histones into the chromatin. However, mechanisms by which histone codes are maintained properly in the newly incorporated histones still remain largely elusive. p53 is known to antagonize K27-trimethylation of histone H3 subunit (H3K27me3) at certain genome loci. Here we show that p53 exploits a hitherto unknown mechanism to maintain histone code in the replicated chromatin. We found that silencing of TP53 (encoding p53) causes an accumulation of H3K27me3 at the nuclear periphery in different human cancer and normal cells, whereas H3K27me3 otherwise mostly localized inside the nucleus. This phenomenon was recaptured in p53−/− mouse embryonic fibroblasts, in which the abnormal H3K27me3 distribution was restored upon expression of p53. The transcriptional activity of p53 was dispensable to this restoration. Super-resolution imaging and biochemical analysis revealed that the perinuclear H3K27me3 was substantially devoid of DNA, but mostly co-localized with the nuclear lamina. We then found that perinuclear enrichment of H3K27me3 is prominent during S phase, rather than other phases of the cell cycle. Polycomb repressive complex 2 (PRC2) propagates H3K27me3 into the replicated chromatin by using parental H3K27me3 as a template, in which EZH2 is the catalytic subunit. H3.1 isoform is the “replicative histone H3” to be synthesized exclusively during S phase and transported into the nucleus. We then found that p53 reduces EZH2 levels in the H3.1 interactome during S phase. Consistently, silencing of EZH2 abolished perinuclear accumulation of H3K27me3 in p53-deficient cells, whereas total H3K27me3 levels and subnuclear localization of EZH2 were not notably changed by the loss of p53. Therefore, it is likely that in the absence of p53, H3.1 may easily be captured by EZH2. Such an unnecessarily trimethylated H3.1 would be isolated at the nuclear lamina so as not to be engaged in the chromatin structure (i.e., rolled up with DNA), although biological relevance of this model needs to be clarified. Our results delineate a novel mechanism of p53 as a guardian of genome integrity, in which p53 appears to antagonize EZH2 to prohibit unnecessary H3K27me3 at the newly formed chromatin during DNA replication.

Keywords: p53, EZH2, H3K27me3, replication

Development of a new combinational epigenetic therapy of multiple myeloma

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Multiple myeloma (MM) is a genetically complex disorder caused by monoclonal proliferation of abnormal plasma cells. Despite development of a variety of new therapeutic agents, MM is still an incurable disorder. Epigenetic alterations including aberrant DNA methylation and histone modifications play key roles in the pathogenesis of MM. We have previously shown that inhibition of a histone lysine 79 methyltransferase DOT1L exerts strong anti-myeloma effects, suggesting that histone methylation could be a therapeutic target in MM. In the present study, we aimed to further clarify the therapeutic potential of histone methylation modifier inhibitors. We treated a series of myeloma cell lines with various combinations of inhibitors against LSD1, G9a, EZH2, JMJD3 and DOT1L, and found that a combination of G9ai and EZH2i strongly suppressed proliferation of multiple myeloma cell lines. Dual inhibition of G9a and EZH2 resulted in reduced levels of mono- and di-methylation of histone H3 lysine 9 (H3K9) as well as mono-, di- and tri-methylation of H3K27. We are currently investigating target genes affected by the dual inhibition in myeloma cells.

Keywords: histone methylation, multiple myeloma
Deep sequencing uncovered initial and fate-determining mutations in well-differentiated neoplasias of the stomach

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Gastric cancer (GC) management is moving toward early detection and early treatment; there is a rising need to understand the molecular profiles of small-sized intramucosal gastric lesions. We collected 43 well-differentiated gastric intramucosal neoplasias (GINs), such as dysplasia/intraepithelial neoplasia (D/IEN) and well-differentiated minute GC (miGC; ≤10 mm), and performed targeted deep DNA sequencing of 67 GC-related genes derived from large-scale data. The most frequent mutations in D/IENs included APC (19/25; 76%), ARID2 (6/25; 24%) and MUC6 (5/25; 20%). ARID2 mutation always co-occurred with APC mutation, whose tumor variant allele frequency (TVAF) was higher than that of ARID2 in D/IEN. APC and TP53 mutations were mutually exclusive in D/IEN (p = 0.031 [main cohort], p = 0.025 [expanding cohort]). TP53 mutations were highly recurrent (11/14; 79%) in MLH1-positive miGCs and were detected even in two microscopic lesions measuring 1 and 3 mm, respectively. Furthermore, TVAF analyses suggested that TP53 mutation is the initial event in the TP53-mutated miGCs. In contrast, TP53 mutation was absent (0/4) in MLH1-negative small intramucosal carcinoma (8-24 mm). Advanced GC data suggested that early mutations (APC and TP53) may affect the potential of cancerous progression from D/IEN. Our results suggest that molecular subtyping based on APC/TP53 mutations would be a high-priority approach for determining and predicting the malignant potential of well-differentiated GIN, including D/IEN.

Keywords: gastric cancer, dysplasia, mutation, carcinogenesis

Artificial intelligence predicts the genetic information of the integrated diagnosis of brain tumors

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The surgical and post-operative management of the central nervous system (CNS) tumors, varies depending on their histologic subtypes or gene informations. Distinguishing glial or non-glial tumor, especially high grade glioma or lymphoma is very difficult to differentiate. And if the tumor is high grade glioma, isocitrate dehydrogenase 1/2(IDH1/2) status will be required for integrated diagnosis of WHO, and O-6-methylguanine-DNAmethyltransferase (MGMT) status for estimating the therapeutic reactivity or prognosis.

Our group used deep neural learning software with GPU accelerated PC, to predict the brain tumor integrated diagnosis without IHCs nor genetic information. We prepared HE slides of the brain tumors submitted to our faculty for diagnosis, gliomas and CNS lymphomas, diagnosed by one or more well-trained pathologists, using FFPE-HE and IHC (GFAP and/or CD20) slides, most of gliomas had information about gene sequencing for IDH1/2 mutation, 1p-19q codeletion by FISH, and MGMT status by immunohistochemistry (IHC).

To build those learning dataset, 256x256 pixel square JPEG image tiles, were automatically extracted by our software. Those images are directly transmitted to the machine learning system, Linux based PC with nVidia GPUs, and deep learning software.

Once the system had learned those images, can classify brain tumor cases, not used for teaching deep learning system dataset, with very high accuracy rates, glioma or and lymphoma. And also, if the case is glioma, AI can predicts the gene information, 1p-19q codeletion, IDH1/2 mutation and MGMT status.

If the pathologic laboratory of the faculty already has a WSI scanner for telepathology, additional cost is only for these GPU and installation, AI-based system will be the most effective aid for the brain tumor diagnosis as telepathology or consultation.

Keywords: Machine learning, Artificial intelligence, Brain tumor, Integrated diagnosis, Classification
The expression of Wnt5a on tumor cell membrane is associated with favorable pathological features and prognosis in hepatocellular carcinoma

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Background: Wnt signaling pathway includes canonical pathway and non-canonical pathway. Wnt/β-Catenin pathway as canonical pathway is associated with the development and progression of hepatocellular carcinoma (HCC). On the other hand, the association between aberrant activation of non-canonical pathway activated by Wnt5a and carcinogenesis or tumor progression of HCC is not well-known.

Methods: We retrospectively screened 243 patients who underwent hepatic resection for HCC. Immunohistochemical staining of Wnt5a was performed on the specimen. Wnt5a positive was defined according to the immunoreactivity on the cell membrane regardless of cytoplasmic immunoreactivity. We investigated whether the expression of Wnt5a correlated with the clinicopathological factors, survival, and recurrence in HCC patients.

Results: The Wnt5a expression was positive in 63 patients (25.9%) and negative in 180 patients (74.1%). The Wnt5a positive was significantly associated with HCV negative (P=0.011), well differentiation (P<0.001), and vascular invasion negative (P=0.046). By univariate analysis, AFP level (P=0.018), PIVKA-II level (P=0.049), tumor number (P=0.013), tumor size (P=0.001), vascular invasion (P=0.001), cirrhosis (P=0.012), and Wnt5a negative (P=0.020) were identified as significant prognostic factors of OS. However, there was no significant difference between Wnt5a positive group and negative group in disease-free survival (P=0.089). Multivariate analysis of OS showed that Wnt5a negative (HR 1.895, 95% CI 1.053-3.409, P=0.033) was identified as an independent prognostic factor. OS after recurrence in Wnt5a positive group was significantly better than negative group (P=0.026), despite the recurrence patterns, treatments for recurrence and time to second relapse had no difference between them.

Conclusions: The expression of Wnt5a on tumor cell membrane is associated with favorable pathological features such as well differentiation and vascular invasion negative, and is independent good prognostic factor in HCC patients. Moreover, the prognosis after recurrence is better in the Wnt5a positive patients than negative.

Keywords: Wnt5a, hepatocellular carcinoma, immunohistochemistry

Identification of gene sets inferring the survival of lung adenocarcinoma

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Lung cancer is the most common cause of cancer death. We tried to develop the risk score to predict the survival of lung adenocarcinoma patients using the gene expression data in The Cancer Genome Atlas (TCGA) dataset.

We screened the prognosis indicator genes in combination with cox univariate regression and multivariate regression. The five genes were used to calculate the risk score. The patients with high risk score showed shorter overall survival and disease-free survival than the patients with low risk score. Multivariate analysis revealed that the risk score is an independent prognosticator compared with stage, smoking status, age, and gender.

Furthermore, we have succeeded to predict the outcome of other microarray datasets (GSE30219 and GSE50081) using the risk score.

Taken together, we identified the risk staging model for lung adenocarcinoma patients using the expression levels of five genes.

Keywords: Lung adenocarcinoma, transcriptome, prognosis
**Integrated therapeutic strategy for lethal tumors**

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Precision Medicine mainly by next-generation DNA sequencing (NGS) revolutionized cancer therapy and is being deployed to guide clinicians in decision-making for cancer treatment. The precise prediction of the effect of each molecular targeting drugs requires molecular alterations at multiple levels such as not only genome, but also epigenome, transcriptome, proteome, and metabolome. Multi-omics requires finest quality of specimens and highest level of bioinformatics. 3D organoid culture model has emerged as promising model for predicting drug efficiency and generating new therapies.

In Hokuto Hospital, we performed NGS for all cancer patients for free and established primary 3D organoid cell lines for all cancer patients as well. After establishing 3D organoid cell line, we quickly performed drug screening, which the drugs are targeted by NGS.

Using these technologies, we can find out "What" should we deliver to the tumor. But the next problem is "How" to deliver. Although many people have been developing drug delivery vehicles, drug-delivery-related problem has not been solved due to the trapping by reticuloendothelial system such as liver before arriving at the targeted site, escaping from immune system and lack of sufficient affinity to the tumor cell surface.

The MRI guided focused ultra sound (MRgFUS) may offer an alternative drug delivery option to achieve proper drug localization at the site of action in a controlled manner. In combination with microbubble and MRgFUS, local and temporal vasculature opening can be achieved. It allows anticancer agents to leak out from local opened vasculature and, as a result, the local drug concentration will be much higher than without vasculature opening. It enable us to reduce total amount of anticancer drugs and adverse side effect. The combination of MRgFUS and 3D organoid technology shed light on a new cancer therapy.

**Keywords:** NGS, DNA sequencing, 3D organoid, Drug screening, Focused ultra sound, Vasculature opening, Drug delivery

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**Identification and functional analysis of a long noncoding RNA associated with chronic gastritis and gastric cancer**

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Long noncoding RNAs (lncRNAs) play important roles in a wide range of biological processes. However, few studies have reported the involvement of lncRNAs in chronic inflammation and their association with carcinogenesis. We aimed to understand the role of long non-coding RNAs (lncRNAs) in the inflammation-related carcinogenesis.

To this end, we searched for lncRNAs associated with gastritis and gastric cancer (GC). Genome wide profiling of histone H3 lysine 4 trimethylation (H3K4me3) identified elevated expression of LUGGC1 (LncRNA Upregulated in Gastritis and Gastric Cancer 1) in the gastritis mucosa of GC patients as well as in GC cells. Knockdown of LUGGC1 affected GC cell proliferation, migration, invasion and in vivo tumor formation, suggesting its oncogenic role. Microarray analysis revealed that LUGGC1 knockdown suppressed expression of interferon-stimulated genes (ISGs), while LUGGC1 overexpression upregulated ISGs. By performing RNA pull-down assay and mass spectrometry, we identified that LUGGC1 interacts with PURA and YB1, which are multifunctional DNA/RNA binding proteins involved in transcriptional and translational regulation. We found that depletion of PURA and YB1 also suppressed GC cell proliferation, suggesting that LUGGC1 may play an oncogenic role by interacting these proteins. Our results suggest that upregulation of LUGGC1 may be associated with the development of GC, and could be a potential therapeutic target.

**Keywords:** Long noncoding RNA, gastric cancer, gastritis
Analysis of expression patterns of microRNAs in ovarian high-grade serous carcinoma

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Background. Although many microRNAs (miRNAs) expression analyses using a fresh frozen samples or cell lines of ovarian cancer already were reported, no analysis of expression patterns of miRNAs in separate components of cancer cell and cancer stromal cell has been studied. Aim of this study was to identify the miRNAs expression status of cancer cell and the surrounding stromal cell, and consequently evaluate ovarian carcinogenesis at the cancer microenvironment.

Methods. Cancer cells and the surrounding cancer stromal cells were obtained from 10 cases of ovarian high-grade serous carcinoma (OHGSC) using a crypt isolation method. Three cases of normal fallopian epitheliums and the stroma were used as a control. Comprehensive analysis of miRNAs using a GeneChip miRNA 4.0 Array (Thermo Fisher Scientific, Inc.) was performed in both components of cancer cells and the surrounding stromal cells.

Results. There was significant difference in the expression of microRNAs between the normal epithelium and the cancer cells in 14 miRNAs examined. In addition, 14 miRNAs originated from cancer stromal cells showed a similar difference in the miRNA expression, compared with the normal stromal cells. In the 28 miRNAs, 3 miRNAs (hsa-miR-34b-5p, hsa-miR-424-3p, and hsa-miR-10a-5p) were commonly found between cancer cells and the stromal cells.

Conclusion. The recent results suggested the miRNA expression pattern of cancer cell were different from those of stromal cells in OHGSC. Such expression pattern of miRNA may play an important role in the form of microenvironment.

Keywords: ovarian cancer, micro RNA, crypt isolation method

H3K27M mutation and prognosis in spinal cord gliomas

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Background and aim: Gliomas harboring H3K27M mutation is classified as “diffuse midline glioma, H3K27M-mutant” in WHO classification revised in 2016, which frequently arise in midline structure such as brainstem, thalamus and spinal cord. The aim of this study is to analyze H3K27M mutation and prognosis in all grades of spinal cord gliomas.

Material and Method: Patients with spinal cord gliomas who have undergone surgery in Hokkaido Univ. Hospital were included in this study. Direct sequencing using DNA extracted from frozen or formalin-fixed paraffin-embedded samples was performed for screening of K27M mutation in H3F3A and HIST1H3B gene. Clinical data was retrospectively reviewed from patient's medical record.

Results: Thirty-four cases of spinal cord gliomas including 6 cases of WHO grade 4, 8 cases of grade 3, 12 cases of grade 2 and 8 cases of grade 1 were analyzed. Conventional pathological diagnosis based on morphology was correlated with patient's survival (p < 0.05). Cases with WHO grade 1 presented favorable outcome with no death during follow-up period, while there were no apparent survival difference between grade 3 and 4. H3K27M mutation was detected in 7 cases including 4 cases of grade 4 (66.7%) and 3 cases of grade 3 (37.5%), and was not detected in grade 1 and 2. One case of grade 3 was diagnosed as grade 2 in initial biopsy surgery. All H3K27M mutation was detected in H3F3A gene. Two-year overall survival in H3K27M group was 60%, and no statistical significance was observed between H3K27M and H3K27-wild type among WHO grade 3 and 4 cases.

Conclusion: H3K27M mutation was not considered as prognostic factor in spinal cord gliomas. Integrated diagnosis with conventional pathology and mutational status in H3K27 would be necessary in spinal gliomas.

Keywords: spinal cord glioma, glioblastoma, H3K27M, diffuse midline glioma, H3F3A
Intracranial vasculopathy after radiation therapy for malignant tumors

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Introduction: Radiation therapy is a standard treatment for malignant brain and paranasal sinus tumors. However, radiation therapy around the intracranial region has a risk of delayed vasculopathy. Here, we report two cases of intracranial vasculopathy resulting from radiation therapy.

Case 1: A 3-year-old girl had received 46.8 Gy of postoperative radiation for paranasal Ewing’s sarcoma. Cerebral angiography 6 years after completion of the radiation therapy revealed progressive cerebral arterial stenotic disease involving the middle cerebral artery (MCA) on the left side. The patient was diagnosed with quasi-moyamoya disease.

Case 2: A 51-year-old female had received 56 Gy of postoperative radiation for glioblastoma. Six years after completion of radiation therapy, sudden onset of conscious impairment occurred as a result of subarachnoid hemorrhage. Computed tomography angiography revealed a fusiform MCA aneurysm. The aneurysm was then clipped, and tumor recurrence was not observed around the aneurysm. The patient was bedridden and received acute medication and rehabilitation.

Discussion: Post-radiotherapy vasculopathy may develop as a result of endothelial damage. For glioblastoma, malignant glioma might cause endothelial proliferation, telangiectasia, and fibrosis on adjacent small vessels. Malignant tumors sometimes have an excellent long-term prognosis, and risk management of late complications is of clinical importance when considering the radiotherapeutic strategies.

Conclusion: De novo vasculopathy can develop while treating a malignant tumor, although the precise pathophysiology remains unknown. The incidence of late vascular complications following radiotherapy might be affected by improved technology, therapeutic interventions, and appropriate follow-up.

Keywords: malignant tumor, vasculopathy, aneurysm, moyamoya

Stroke mimics and chameleons caused, or characterized, by glioma

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Introduction: Gliomas are sometimes difficult to differentiate from stroke and are often misdiagnosed on magnetic resonance imaging (MRI); thus, the terms “stroke mimics” (false-positive stroke diagnosis) and “stroke chameleons” (false-negative stroke diagnosis) have been introduced. In this study, we analyzed stroke mimics and stroke chameleons in glioma, and discussed the tendency for misdiagnosis.

Methods: We retrospectively reviewed the pathological specimens that were removed from the lesion that was considered to be a brain tumor. This study enrolled 144 patients who underwent tumor resection or biopsy preoperatively for suspected glioma at Sapporo Medical Univ. between January 2012 and December 2017. Characteristics of the patients including age, sex, image findings, and stroke type were compared between stroke mimics, stroke chameleons, and glioma.

Result: Stroke chameleons and stroke mimics tended to occur in older patients compared with glioma (p=0.012). In both stroke chameleons and stroke mimics, the lesion showed hyperintense signal intensity on T2-weighted imaging and FLAIR-sequence MRI. The average time between primary radiological diagnosis and pathological diagnosis was 13.8 days in stroke chameleons and 60.2 days in stroke mimics, which was significantly different (p=0.016). Based on these findings, MRI follow-up before pathological diagnosis should be performed within 2 months in patients with suspected stroke mimics caused by glioma.

Conclusion: Gliomas affect the patient’s prognosis and should be diagnosed as soon as possible. However, misdiagnosis, such as stroke mimics that are caused by glioma, can occur. In these patients, introduction of the treatment will be delayed, and the patient might be beyond cure. The diagnosis of stroke should be made as quickly as possible, taking into consideration the possibility of a glioma in clinical situations.

Keywords: glioma, stroke, misdiagnosis
[P-25]  
**Generation and functional analysis of 5-FU resistant gastric cancer organoids**  
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Gastric cancer (GC) often acquires drug resistance and 5-FU is one of the key drugs in the treatment of GC. Although several evidences have demonstrated that cancer stem cells (CSCs) play a key role in the acquisition of drug resistance, the detailed mechanism how CSCs endure the environment with anti-cancer drugs remain unknown. Organoid is a novel 3D cell culture system through using the specific niche factors in a dish. Since organoid is believed to harbor abundant stem cells, cancer organoid could possibly be useful for scrutinizing CSC biology. In this study, we established GC organoids (GCOs) from patient derived specimens, and gradually treated them with increasing concentrations of 5-FU in order to establish 5-FU resistant GCOs. We have successfully harvested three 5-FU resistant GCOs that can stand 3 times higher dose of 5-FU than IC50 of 5-FU in parental GCOs. 5-FU resistant GCOs showed distinct changes that closely resemble the morphological features of CSC. We also found that 5-FU resistant GCOs showed higher levels of expression of several stem cell markers and key molecules related to 5-FU metabolism compared to their parental GCOs. We then performed microarray analysis using 3 pairs of 5-FU resistant and parental GCOs and narrowed down 23 genes through the comparison of expression profiles between 5-FU resistant GCOs and 5-FU resistant cell lines. Further validation revealed that MYBL1 and KHDRBS3 are more likely to be involved in the acquisition of 5-FU resistance in CSC. In silico analysis using KM-plotter figured out that high levels of expression of both MYBL1 and KHDRBS3 were significantly associated with worse clinical outcome in GC patients.  
Keywords: Gastric Cancer, Organoid, Cancer Stem Cell, 5-FU, Drug resistance

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[P-26]  
**New micro-cell culture platform “micro/nanoplate” induces self-organization of microtumor in PDACs**  
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Pancreatic ductal adenocarcinoma (PDAC) is still one of the most lethal malignant cancers. In our previous study, when PDAC cells were cocultured with epithelial feeder, they formed anchorage-dependent multicellular aggregates (Ad-MCAs) and acquired further intractable properties. Current 3D cell culture systems are mostly anchorage independent and do not mimic much of the pathological features of aggressive cancer. In this study, we visualized dynamics of live-PDAC microtumor using micro-cell culture platform, micro/nanoplates. When PDAC cells were cultured on the micro/nanoplates overnight, they self-organized into non-spheroidal microtumors that were anchored to the plate through cell-in-cell invasion (entosis). Similar structures of microtumors were frequently observed in human PDAC specimens. Furthermore, microtumors actively stretched to catch dead cell debris using lamellipodia and endocytose debris-derived surface nucleosides directly into vacuoles (resulting in PS externalisation, a cause of cancer immune evasion). These results suggest that the tumor dynamics visualised by our simple technology urge us to review the well-known pathogenesis of this intractable cancer and will contribute to the development of innovative new anticancer drugs.  
Keywords: PDAC, self-organized, micro/nanoplates, microtumors, cell-in-cell invasion  

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Novel drug-screening system using hydrogel-induced cancer stem cells

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Cancer tissue is composed of heterogeneous cells, in which cancer stem cells (CSCs) are the important factor regulating the heterogeneity because of their multipotency and self-renewal ability like normal tissue stem cells. CSCs have the chemotherapeutic and radiotherapy-resistance and being source of recurrence; therefore, establishment of novel therapeutics targeting CSCs should be urgent issue in worldwide. However, the detection of CSCs is difficult owing to a few numbers of them in cancer tissues. Recently, we developed the novel and rapid CSC-induction method using double-network (DN) hydrogel composed of poly-2-acrylamido-2-methylpropanesulfonic acid (PAMPS) and poly-N,N'-dimethylacrylamide (PDMAAm).

To apply the DN gel-based CSC induction method for the selection of CSC-specific therapy, drug screening with 288 chemical compounds was performed in human glioblastoma (GBM) cell line KMG4 cells cultured on DN gel, polystyrene (PS) dish as normal culture condition, and poly-acrylamide (PAAm) gel which induced sphere formation but not inducing the mRNA expression of stemness-associated genes Nanog, Oct3/4, and Sox2. In KMG4 cells on DN gel, 14 compounds were detected as drugs which might be effective targeting GBM stem cells in comparison with on PS dish and PAAm gel within 72 hours.

These results revealed that the DN gel-based CSC induction method might be useful for the rapid selection of CSC-specific drugs.

Keywords: Cancer stem cells, Biomaterial, Drug screening, Glioblastoma

Induction of cancer stem cell properties through mechanosensitive ion channels

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Ability of tumor formation is defined by a small group of cancer stem cells (CSCs), which leads to the tumor recurrence, metastasis, and acquisition of drug resistance after initial treatment of the malignancy. When targeting CSCs, an elucidation of the molecular mechanisms involved in the maintenance of CSCs is important; however, it is difficult due to a few numbers of CSCs in tumor. Recently, we showed a novel method to inducing stemness of tumor cells with double-network (DN) hydrogel composed of poly-(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) and poly-(N,N'-dimethylacrylamide) (PDMAAm). KMG4 glioblastoma cells cultured on DN gels formed stem cell-like spheres and increased mRNAs such as SOX2, Nanog, Oct3/4 and OPN, and increased tumorigenicity when transplanted into mice. This suggests that DN gels mimic microenvironment of CSC niches, in which the tumor cells might receive stimuli from the DN gel through mechanoreceptors. Here, to identify the mechanoreceptors important for the CSCs induction, we focused on transient receptor potential cation channel (TRP), because the expression levels of TRPM4, TRPV1, and TRPV2 mRNAs were especially high in the KMG4 cells. KMG4 cells were pretreated with 2-aminoethoxydiphenylborane (2-APB) as an TRP inhibitor, followed by culturing on DN gels for 8 hours, which failed to increase the mRNA expression of OPN. This suggests that TRPs play an important role in inducing the CSCs on DN gels, which might be a critical therapeutic target inhibiting CSCs in in vivo tumor.

Keywords: cancer stem cells, hydrogel, biomaterial, mechanoreceptor, TRP
**Development of the cryogel for neuronal tissue engineering**

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**Introduction:** Central nervous system has limited regenerative capacity. The stroke, neural degeneration, or brain surgery for brain tumor end up failing the brain functions, and unfortunately, current treatment strategies are insufficient to recover the lost functions. Some biomaterials for the neural regeneration were reported in this decade, however, they didn’t achieve enough recovery of lost functions. We present the new material ‘porous, soft and flexible hydrogel’ for neural regeneration.

**Materials and Methods:** For cryogels, the acrylamide-based anionic AMPS monomer with sulfonic residue and cationic APTMA monomer with trimethylammonium residue were polymerized in the freezer (-16°C). After thawing and washing the freezing regions, the porous structure was obtained. Total monomer concentration was 1.0 or 0.5 mol/L and crosslinker concentration was 1.0 mol%. The stiffness was measured as compressed Young’s modulus. Neural stem cells (NSCs) were cultivated in these cryogels and evaluated cell adhesion, proliferation, and differentiation.

**Results:** The stiffness of the cryogel were 1.6 kPa (monomer concentration was 0.5 mol/L) and 3.2 kPa (1 mol/L) with flexibility. NSCs efficiently attached to the cryogel, and moved into the pore. Immunofluorescence analysis revealed the 3D network composed of astrocyte, oligodendrocyte, and neuron.

**Discussion:** The cryogel with soft stiffness near the brain (about 1.0 kPa) exhibits flexible structure. These physical properties may be suitable in the brain. The porous structure also allowed neural cells to form a 3D network. These results showed this cryogel might be a useful scaffold after the brain injury. We plan to perform in vivo assay, transplantation the cryogel into the mouse brain for the evaluation of the cell migration and axonal extension.

**Conclusion:** We made the new material for neural regeneration, which provides neural stem cells with the scaffold to reconstruct the 3D network.

Keywords: neural tissue engineering, cryogel, hydrogel, neural stem cell

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**A whole-animal platform for developing novel anti-cancer drug leads**

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Kinase inhibitor drugs have demonstrated benefits for some patients but often at the cost of significant toxicity and dosing problems. Here, we present a multidisciplinary approach for developing improved drug analogs within a whole-animal context using Drosophila. We combine chemical and genetic modifier screening with computational modeling to develop new analogs of the approved kinase inhibitor sorafenib within an established Drosophila model for RET-dependent medullary thyroid carcinoma (MTC). Resulting tumor calibrated inhibitors (TCIs) have reduced activity towards ‘anti-targets’ MNK1 and BRAF therefore enhanced Ras pathway inhibition, and exhibit strongly improved therapeutic index in whole animal fly and human MTC xenograft models. Applying this platform to a variety of cancers can provide a rational path forward for the development of new classes of high efficacy/low toxicity drugs.

Keywords: kinase inhibitor drugs, medicinal chemistry, Drosophila, chemical genetic screening, anti-target
Increased ABCB1 expression in tumor blood vessels of urothelial carcinoma after chemotherapy

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ABCB1, ATP binding cassette transporter, one of the stem markers, plays a major role in drug resistance. We reported that tumor endothelial cells (TECs) are resistant to paclitaxel (PTX) with ABCB1 upregulation. Gemcitabine/Cisplatin (GC) is a standard 1st line chemotherapy for metastatic urothelial carcinoma. PTX is often selected as 2nd line chemotherapy for GC resistant cases; however, the therapeutic outcomes are limited. We hypothesized that TEC ABCB1 is the cause of this situation. In this study, we investigated ABCB1 expression in 66 cases which were resected before and after 1st line chemotherapy by ABCB1 and CD31 immunostaining. In 42 cases (64\%), the ratio of ABCB1+ TECs increased after 1st line chemotherapy, but not in tumor cells. High ABCB1 expression in tumor blood vessels was correlated with poor prognosis. As the mechanism, chemotherapy elevated ABCB1 expression levels in ECs via increasing tumor IL-8 secretion. In vivo assay, when the ABCB1 inhibitor was combined with PTX, tumor growth and metastasis were more reduced with anti-angiogenic effect compared to PTX alone. It was suggested that chemotherapy causes inflammatory changes in tumors, which induce ABCB1 expression in TECs and cause drug resistance. Targeting ABCB1 in TECs can be a new strategy to overcome cancer drug resistance.

Keywords: Tumor angiogenesis, Drug resistance, ABCB1

Carbonic anhydrase 2 (CAII) is essential for tumor endothelial cell proliferation under various metabolic conditions

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Tumor glycolytic activity leads to the production of high quantities of lactic acid which may adversely affect stromal cells including endothelial cells, which are responsible for the formation of tumor blood vessel to support tumor growth and metastasis. However, the mechanisms by which tumor endothelial cells (TECs) survive high lactic acid levels to promote tumor angiogenesis in tumors remains unknown. We investigated the molecular factors which influence the adaptation of TECs to lactic acidosis in this study. Metabolomic analysis showed differences in TECs and normal endothelial cell (NECs) metabolomes. Glycolysis was more activated in TECs than NECs and TECs proliferated more in lactic acidosis than NECs. qRT-PCR analysis revealed the upregulation of various pH regulators including the endothelium-associated carbonic anhydrase II (CAII) in TECs. CAII was expressed in murine and human tumor endothelia. Subsequent CAII knockdown inhibited TEC proliferation, while, in vivo inhibition of CAs with acetazolamide minimally reduced tumor blood vessel density but increased the number of matured blood vessels in the tumors. Additionally, acetazolamide-treated mice showed a reduction in lung metastasis. Together, the findings indicate that CAII plays a significant role in TEC proliferation, furthermore, targeting CAs may improve cancer therapy potentially via enhanced drug delivery in matured vessels.

Keywords: angiogenesis, tumor endothelial cells, carbonic anhydrase 2, lactic acidosis, glycolysis
Macrophage-mediated transfer of cancer-derived components to stromal cells in gastric cancer

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Tumor-derived extracellular vesicles (TEVs) secreted into the blood create a pre-metastatic niche in distant organs; however, it is unclear how TEVs are delivered and how they affect stromal cells in the tumor microenvironment. Tumor-associated macrophages (TAMs) play pivotal roles in cancer progression by interacting with cancer cells and other stromal cells. Here, we present a novel function of TAMs: delivery and transmission of TEV contents. TEV-incorporating macrophages (TEV-MΦs) showed increased invasiveness and were disseminated widely. Upon contact with host stromal cells, TEV-MΦs released membrane blebs containing TEVs. Scattered blebs were incorporated into stromal cells, leading to transfer of cancer-derived RNA and proteins. TEV-MΦ-secreted blebs containing cancer-derived components contributed to myofibroblastic changes in recipient stromal cells. These results suggest a novel function for TAMs: transfer of cancer-derived components to surrounding stromal cells and induction of a pro-tumor microenvironment via an increase in the number of CAF-like cells.

Keywords: Tumor-associated macrophages (TAMs), Tumor-derived extracellular vesicles (TEVs), gastric cancer

Cancer-adipose tissue interaction with fluid flow modulate cell kinetics and chemosensitivity in gastric cancer

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Background: Submucosal and subserosal adipose tissue is a frequent site of gastric cancer invasion, but the interaction between adipose tissue and gastric cancer remains unclear. In addition, every cell types in organs are affected by the environmental mechanical forces, such as a fluid flow stress, while the effects of fluid flow stress have not been investigated on the gastric cancer tissue. The aim of this study is to analyze the gastric cancer cell kinetics in the reconstruction model which mimicked cancer-stroma interaction and physical microenvironment.

Methods: To replicate cancer-stroma microenvironment, gastric cancer cell (MKN7 and MKN74) were seeded on the rat adipose tissue fragments embedded disc or the collagen disc alone. To generate fluid shear stress, samples placed on a rotatory shaker in the CO2 incubator. Proliferation, apoptosis, invasion and motility related molecules were analyzed by the morphometry and the immunostaining. Proteins were assayed by Western blot analysis.

Results: Adipose tissue promoted the hypertrophy and proliferation of gastric cancer cells, and the fluid flow stress synergistically amplified these effects. Finally, the cancer layer became thickened and cancer cells invaded into collagen disc. Adipose tissue significantly accelerated the proliferating cell number and inhibited cleaved-caspase 3 expression in gastric cancer cells. Adipose tissue promoted expression of MAPK (ERK 1/2, p-ERK1/2), and inhibited the expression of p-p38.

Conclusion: We demonstrated that cancer-adipose tissue interaction and physical microenvironment have mutual affect for the gastric cancer cell kinetics and chemosensitivity.

Keywords: gastric cancer, adipose tissue, fluid flow, chemosensitivity
Alteration of the immunosuppressive population after neoadjuvant therapies for locally advanced rectal cancer

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[Background] Although neoadjuvant chemoradiation (CRT) is thought to be the standard neoadjuvant therapy for locally advanced rectal cancer, in recent, the benefits of neoadjuvant chemotherapy (NAC) has also been reported. The mechanism of immunosuppressive cells in the antitumor effect of these neoadjuvant therapies has not been elucidated. In this study, we investigated the alteration of immunosuppressive cells after CRT and NAC.

[Methods] Two-hundred rectal cancer patients were enrolled and categorized into three groups according to pretreatments: CRT (n=48; 5-FU or Capecitabine + Radiation), NAC (n=51, FOLFOX), Surgery alone (n=101). The status of regulatory T-cells and myeloid-derived suppressor cells were assessed by the multiplex fluorescence immunohistochemically analysis.

[Results] Using CD3, CD4, and Foxp3 expression, the regulatory T-cells were evaluated. Compared with surgery alone, both CRT and NAC significantly decreased the proportions of Foxp3-high cells in CD3+CD4+ cells. On the other hand, when we assessed the M2 macrophages using CD68 and CD204 expression, the densities of CD68+CD204+ cells were significantly increased by NAC, but not CRT. Regarding pathological complete response cases (CRT: n=7, NAC: n=5), the proportion of Foxp3-high cells were significantly less compared to residual tumor cases after NAC, not significantly after CRT. However, the densities of CD68+CD204+ cells were comparable between cases with residual tumor and no residual tumor.

[Conclusions] Our results suggested that neoadjuvant therapies for rectal cancer can elicit effective responses by a decrease in the regulatory T-cells population, and cannot be sufficient for the depletion of myeloid-derived suppressor cells. We think that additional approaches for the depletion of myeloid-derived suppressor cells would be needed for the improvement in the antitumor response.

Keywords: rectal cancer, neoadjuvant therapy, regulatory T-cells, myeloid-derived suppressor cells, M2 macrophage

Synergistic cytotoxicity of oncolytic adenovirus in combination with cisplatin chemotherapy

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The combination of oncolytic adenoviruses and specific chemotherapy agents is a novel approach for human cancer therapeutics. A detailed analysis of the network between adenovirus and chemotherapeutic agents can help design an effective strategy to combat cancer.

AU-rich elements (ARE) are RNA elements that enhance the rapid decay of mRNA. ARE-binding proteins control the fate of ARE-mRNA. HuR is a RNA binding protein, which is involved in the export and stabilization of ARE-mRNA. HuR constitutively relocates to the cytoplasm in cancer cells, resulting in the stabilization of ARE-mRNA. Previously, it was reported that the adenovirus gene product, E4orf6 is necessary for virus replication, participates in ARE-mRNA export and stabilization. Recent report unveiled that E4orf6 is not required for virus replication in cancer cells, where ARE-mRNA is always stabilized. In this study, we sought to investigate whether a combined treatment of E4orf6 gene deleted oncolytic adenovirus, dl355 and cisplatin can have an enhanced cell-killing effect on cancer cells.

In vitro experiments showed that dl355 enhance cisplatin induced apoptosis and causes remarkable cancer cell death in several types of cancer cells. Apoptosis induction by treatment with dl355 and/or cisplatin was detected in cancer cells by apoptotic cell staining, flow cytometry, and western blot analysis. In addition, enhancement of cancer cell death in combination therapy was assessed by the XTT assay and cytopathic effect (CPE) assay. Notably, in a mouse xenograft model, dl355 and cisplatin combination inhibited tumor growth.

These data strongly suggested that dl355 and cisplatin co-treatment might serve as an effective therapeutic strategy against cervical cancer.

Keywords: Oncolytic Adenovirus, cisplatin, HuR, ARE-mRNA
CCL8 deficiency in host strongly inhibits early mortality of acute graft-versus-host disease in mice

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Although allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for diverse malignant and nonmalignant diseases, acute graft-versus-host disease (aGVHD) plays a pivotal role in mortality of HSCT. We have previously shown that CC chemokine ligand 8 (CCL8) closely correlates with aGVHD mortality in both human and mice. To study a role of CCL8 in aGVHD, CCL8 knockout mice (CCL8-/-) were transplanted with fully allogeneic marrow grafts. CCL8-/- transplanted with allogeneic graft showed apparently prolonged median survival days from 9 to 45 and resulted in considerable reduction of mortality at day 28 (23.4\% versus 90.0\% survival of recipients, \( p < 0.0001 \)) in wild type versus CCL8-/- recipients, respectively. aGVHD pathology of CCL8-/- were significantly attenuated comparing to those in wild type, though the donor T cell expansion and the plasma level of IFN-\( \gamma \) and TNF-\( \alpha \) during aGVHD was shown to be similar in both type of mice. An abrupt death of CCL8-/- host occurred after 28 days of BMT, which is preceded by a rapid increase of plasma CCL8 of donor graft origin. These findings indicate that CCL8 is intimately involved in aGVHD pathology.

Keywords: hematopoietic stem cell transplantation, GVHD, cancer, CCL8, molecular target

A role for IL-34 in multiple myeloma-induced osteolytic disease

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Div. of Immunobiology, Institute for Genetic Medicine, Hokkaido Univ.

Multiple myeloma (MM) is a hematological malignancy that grows in multiple sites of the axial skeleton and causes debilitating osteolytic disease. Interleukin-34 (IL-34) is a newly discovered cytokine that acts as a ligand of colony-stimulating factor-1 (CSF-1) receptor and can replace CSF-1 for osteoclast differentiation. In this study, we identify IL-34 as an osteoclastogenic cytokine that accelerates osteolytic disease in MM. IL-34 was found to be expressed in the murine MM cell line MOPC315.BM, and the expression of IL-34 was enhanced by stimulation with proinflammatory cytokines or by bone marrow (BM) stromal cells. MM-cell-derived IL-34 promoted osteoclast formation from mouse BM cells in vitro. Targeting IL34 by specific small interfering RNA impaired osteoclast formation in vitro and attenuated osteolytic disease in vivo. In BM aspirates from MM patients, the expression levels of IL-34 in CD138+ populations vary among patients from high to weak to absent. MM cell-derived IL-34 promoted osteoclast formation from human CD14+ monocytes, which was reduced by a neutralizing antibody against IL-34. Taken together, this study describes for the first time the expression of IL-34 in MM cells, indicating that it may enhance osteolysis and suggesting IL-34 as a potential therapeutic target to control pathological osteoclastogenesis in MM patients.

Keywords: Interleukin-34, Multiple myeloma, osteoclastogenesis, Bone lesions
Inhibition of IL-34 production by JQ1 as a novel therapeutic strategy in cancer therapy

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Interleukin-34 (IL-34) acts as an alternative ligand of the colony-stimulating factor-1 receptor (CSF-1R) and controls the biology of myeloid cells including survival, proliferation, and differentiation. In cancer, IL-34 has been reported to be expressed in human cancers and several types of malignant tumor tissues at different levels. Additionally, IL-34 was reported to promote tumor progression and metastasis of certain cancers via promotion of angiogenesis and macrophage recruitment.

It has been reported that targeting IL-34 in chemo-resistant tumors resulted in a remarkable inhibition of tumor grow (Baghdadi M et al. Cancer Res. 2016). Therefore, blocking of IL-34 is considered as a therapeutic strategy to suppress tumor progression. However, the molecular mechanisms that control IL-34 production are still completely unknown. Therefore, we aimed to identify factors responsible for IL-34 production in cancer cells. Furthermore, by targeting the activities of such factors using specific inhibitors or small molecule drugs, its impact on improving the therapeutic effects will be evaluated.

From screening of small molecular compounds, Bromodomain (BRD) and extra terminal (BET) inhibitor JQ1 was found to suppress IL-34 expression, both at mRNA and protein levels, in IL-34 producing mouse ovarian cancer cell line HM-1. Importantly, by preforming the chromatin-IP, we found the recruitment of gene transcription factor BRD4, which is the major target of JQ1, at the promoter of IL-34 gene was significantly decreased by JQ1.

Further studies are still needed, but there is a possibility that BRD4 may play a role in IL-34 production in IL-34 producing ovarian cancer cell line HM-1. In addition, JQ1 may decrease IL-34 highly producing tumor growth by inhibiting IL-34 expression in cancer cells.

Keywords: Interleukin-34, Cancer, BET inhibitor, Bromodomain

The impact of IL-34 on immunotherapy resistance in colorectal cancer

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Interleukin-34 (IL-34) is a cytokine that was discovered in 2008 as a second ligand of Colony stimulating factor 1 receptor (CSF1R) in addition to Macrophage colony-stimulating factor (MCSF). IL-34 controls the biology of myeloid cells, such as survival, proliferation, and differentiation. Importantly, IL-34 plays critical roles in multiple aspect of the tumor microenvironment including cell invasion, metastasis, angiogenesis, tumor growth and immunosuppression. IL-34 is involved in the pathological process of inflammatory diseases such as inflammatory bowel disease (IBD). IBD frequently progress to colorectal cancer (CRC), one of the most common forms of malignancy and the second leading cause of cancer-related death in Japan. Thus, IL-34 is expected to be involved in CRCs. As an immunosuppressive cytokine, IL-34 may impact the clinical outcome of cancer therapy. In this study, we focus on the potential role of IL-34 in suppressing effective antitumor response in the context of CRC immunotherapy.

Keywords: Colorectal cancer, Interleukin-34, Immunotherapy
The potential involvement of Interleukin-34 in metastasis of ovarian cancer

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Interleukin-34 (IL-34) is a novel cytokine that was described as a second ligand of colony stimulating factor-1 receptor (CSF-1R) in addition to CSF-1. IL-34 acts as a key regulator of survival, proliferation, and differentiation of myeloid lineage cells including monocytes, macrophages and osteoclasts. In cancer, IL-34 has important roles in tumor growth, cancer cell invasion, metastasis, and resistance against cancer therapy in several cancers including lung cancer, colon cancer, hepatocellular carcinoma, and osteosarcoma. In this regard, the role of IL-34 in ovarian cancers remains largely unknown. In this study, we examine the potential role of IL-34 in ovarian cancers using a murine ovarian cancer model.

HM-1 is a mouse ovarian cancer cell line with high lymph node metastatic potential. Interestingly, compared to other ovarian cancer cell lines with low or no potential of metastasis, HM-1 shows high expression of IL-34. Thus, we expected that IL-34 may contribute to metastasis in this model. To examine this hypothesis, we generated IL-34 knockout HM-1 cell line using CRISPR-CAS9 system and evaluated its metastatic potential in vitro and in vivo. Interestingly, compared to the wild-type HM-1 cell line which exhibits high potential of lung metastasis, the deficiency of IL-34 resulted in a significant impairment of this potential, accompanied with prolonged survival of mice. Together, these results indicate a role for IL-34 in metastasis of ovarian cancers. Current works focus on identifying the molecular and cellular mechanisms that control IL-34 functions in this model.

Keywords: Interleukin-34, Ovarian cancer, Metastasis

Arginase-1 is related to the malignancy of colon cancer cells

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Arginase-1, a urea cycle-related protein, catalyzes the hydrolysis of arginine to urea and ornithine, which is subsequently metabolized into proline and polyamides. The arginase-1-mediated metabolites are crucial for bioenergetic pathways and regulate proliferation, differentiation and function of cells. Previously, we found that administration of arginase inhibitor into tumor-bearing mice significantly suppressed the tumorigenesis of cancer cells in vivo.

In this study, we investigated whether arginase-1 was directly involved in the proliferation of cancer cells in vitro. Firstly, we cultured CT26 murine colon cancer cells in the presence of arginase inhibitor. The proliferation was evaluated by MTT assay. As a result, inhibition of arginase-1 significantly suppressed the proliferation of CT26 cells in vitro. Next, we established Arg1 gene knockout (KO) CT26 cells by using CRISPR-Cas9 system. The proliferation of Arg1KO CT26 cells was significantly lower compared to the mock control cells. To investigate the effect of arginase-1 on tumorigenesis in vivo, we intradermally inoculated Arg1KO CT26 cells into wild-type BALB/c mice. Knockout of arginase-1 gene in CT26 cells significantly suppressed the tumor growth in our tumor-bearing model.

From these findings, we speculate that arginase-1 plays an critical role in the malignancy of colon cancer cells, suggesting that regulation of arginase-1-mediated metabolism may be a promising target in therapy for patients with colorectal cancers.

Keywords: arginase-1, nor-NOHA, proliferation, colon cancer
Neuropeptide signaling through NK2R is related to malignancy of colon cancer cells

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Neuropeptides, generally distributed in central and peripheral nervous system. Previously, we found that neurokinin-2 receptor (NK2R), a receptor of neurokinin A, was expressed in tumor areas of colorectal cancer patients.

In this study, we examined the functional roles of neuropeptide signaling through NK2R in colon cancer cells. CT26 murine colon cancer cells were treated with a selective NK2R antagonist in vitro. The viability and proliferation of CT26 cells were evaluated by MTT assay. The blockade of neuropeptide signaling by NK2R selective antagonist significantly suppressed the proliferation of CT26 cells. Next, to investigate the effect of neuropeptide signaling on tumorigenesis of CT26 cells in vivo, we intradermally inoculated CT26 cells into wild-type BALB/c mice. The tumor growth was significantly reduced by the administration of NK2R antagonist into the CT26-bearing mice. Moreover, we confirmed that knockout of NK2R gene in CT26 cells significantly suppressed the tumor growth in our tumor-bearing model. Based on transcriptome analysis, we found several neuropeptide signal-related genes regulating tumorigenesis of colon cancer cells.

From these findings, we speculate that blockade of neuropeptide signaling through NK2R and the target molecules may be a promising strategy in effective therapy for colorectal cancer patients.

Keywords: Neuropeptide signaling, NK2R, Malignancy, Colon cancer

Inhibition of diacylglycerol kinase alpha activates anti-tumor effector T cells in tumor-bearing host

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Background: Diacylglycerol kinases (DGKs), lipid kinases transforming diacylglycerol to phosphatidic acid, play important roles in intracellular signal transduction. Diacylglycerol kinase alpha (DGKa), an isozyme of DGKs, is well-known to promote proliferation of cancer cells by suppression of the apoptosis. Additionally, a previous report demonstrated that activation of DGKa induced anergy state of T lymphocytes in vivo. In this study, we investigated whether inhibition of DGKa not only suppress the tumorigenesis of cancer cells but also activate anti-tumor immunity.

Methods: We first investigated the effect of DGKa inhibitor on in vitro proliferation of murine hepatoma cell lines (Hepa1-6) by cell proliferation assay. Cytokine and Granzyme B productions by CD8+ T cells from OT-1 mice after the OVA antigen stimulation were evaluated by ELISA and flowcytometry, respectively. Next, we established a tumor-bearing mice model by injection of mCherry-transfected Hepa1-6 cells into spleen. Tumorigenesis and tumor-infiltrating T cells in the liver were evaluated by in vivo imaging system, HE staining, and immunohistochemistry.

Results: Proliferation of Hepa1-6 cells were suppressed in the presence of DGKa inhibitor in vitro. IL-2 production levels of OT-1 CD8+ T cells in control group was augmented by the addition of DGKa inhibitor (246 vs 579 pg/ml, p<0.05). Granzyme B-positive cells in OT-1 CD8+ T cells were increased by the treatment with DGKa inhibitor compared to the control group (4.4 vs 8.9 %, P<0.05) after the antigen stimulation. In vivo administration of DGKa inhibitor significantly suppressed the tumor size (fluorescence AU 2.0x10^10 vs 6.3x10^9, area (μm2) 1.5x10^7 vs 0.9x10^7, P< 0.05) in the liver of tumor bearing mice. Then, the number of tumor-infiltrating T cells (582 vs 1506, 5 HPF, p<0.05) was elevated by the DGKa treatment.

Conclusions: Inhibition of DGKa not only suppressed the proliferation of hepatoma but also activated anti-tumor effector T cells in vivo.

Keywords: diacylglycerol kinase alpha, hepatoma, anti-tumor effector T cell
Structural changes in peptide-HLA class I complexes predict neoantigen immunogenicity

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Neoantigens presented by HLA on cancer cells are expected to become a therapeutic target and a biomarker of effectiveness. But out of existing 102-103 non-synonymous mutations in exons of cancer cells, a handful of mutations could be presented by HLA and elicit T cell response. The factors that defines immunogenicity is poorly understood.

By means of HLA ligandome analysis combined with genomic data, we detected 4 and 2 neoantigens that were naturally presented by HLA-A24 and A2, respectively, of a colon cancer line HCT15/β2m. A 9-mer neoepitope AKF9 which has a single amino acid substitution (N>K) at P8, was presented by HLA-A24, demonstrating the highest induction rate. To examine the impact of amino acid substitution on T-cell induction rate, we prepared AXF9 peptides which are P8 variants of AKF9 (P,K,I,D,H,S,T,Y) and the wild-type counterpart ANF9. Both the variants and wild-type empirically bound to HLA-A24 equally. Additionally, we made each of the pMHC 3D model structures. We found that compared to ANF9, TCR-oriented structural changes induced by single-amino acid substitution (epitope volume change, EVC) was, if not perfectly, correlated with the responding T-cell induction rate. It is indicated that the EVC may explain the difference of immunogenicity induced by a single-amino acid substitution.

Keywords: Immunogenicity of neoantigen

The inflammation amplifier promotes tumor progression in a mouse model

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Simultaneous activations of NF-kB and STAT3 in non-immune cells result in a hyper-activation of NF-κB pathway, associated with a large amount of chemokine and cytokine productions that lead to chronic local inflammation. This phenomenon is called the inflammation amplifier. We have reported the inflammation amplifier is essential for the development of various chronic inflammatory disease models including those for rheumatoid arthritis and multiple sclerosis. Here, we examined that a relationship between the inflammation amplifier and tumor progression. Using the F759 mice, which are designed to have enhanced inflammation amplifier, we found that these mice have had higher tumor burdens, STAT3-p65 hyper up-regulation and also higher IL6 serum levels, upon B16F1 injection. RNA-Seq analysis revealed that immune-evading molecules including Arg1 were upregulated in the tumor from F759 mice. These results suggest that regulation of chronic inflammation, particularly via the inflammation amplifier, could be used as a target for cancer treatment.

Keywords: Inflammation amplifier, IL-6, F759 mice
Tumor-initiating cell induce immuno-hyporesponsiveness following cellular senescence to macrophages guarantee its tumorigenesis

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In cancer cells, we often undergo the gaps between immortal proliferation in vitro and tumor growth in vivo, especially in immunocompetent animals. Tumor-initiating cell theory that only the special cells among cancer, that is a tumor-initiating cell, have the potential to initiate tumor in vivo, is one of the possible explanations for this controversial phenomenon. Targeting therapy for tumor-initiating cells that can initiate tumor in immunocompetent individuals is considered promising therapy to achieve complete remission. However, it is largely unknown the features of tumor-initiating cells and the phenomena that made by them in the immunocompetent animal. Here we show that the tumor cells that can initiate tumor in immunocompetent animals secrete inflammatory cytokines and induce macrophages into a senescence-like state. Senescent-like macrophages highly express Arginase-1 and induced T cell hyporesponsiveness. Our results indicate that recovering of immune-senescence in a tumor microenvironment is a novel promising therapeutic strategy for cancer therapy.

Keywords: cancer stem cells, tumor initiating cells, immunocompetent animal, immunity, cellular senescence

WPI-Chemical Reaction Design and Discovery (ICReDD) develops highly efficient chemical reactions and the innovative products for all of humanity

WPI-ICReDD Tanaka Lab: Masumi Tsuda1,2,3, Akira Hirota1,2, Masamichi Imajyo1,2, Shinya Tanaka1,2,3
WPI-ICReDD PIs: Shinya Tanaka1, Michael Rubinstein3, Tetsuya Takesugu1, Hiroki Arimura1, Alexandre Varnek5, Ichigaku Takigawa1, Tamiki Komatsuzaki1, Masaya Sawamura1, Benjamin List6, Yasuhide Inokuma1, Yasuchika Hasegawa1, J ian Ping Gong1, Hajime Ito1, Satoshi Maeda1

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Selected to be a part of the World Premier International Research Center Initiative (WPI) by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, Hokkaido University launched the “Institute for Chemical Reaction Design and Discovery (ICReDD)” in October 2018. The ICReDD aims to acquire an in-depth understanding of complex chemical reactions and to accelerate the efficient development of new chemical reactions. The WPI supports the program for ten years, providing seven hundred million yen each year.

Finding new chemical reactions is indispensable for generating advanced materials and chemicals. So far, such development requires a trial-and-error approach which tends to be time-consuming, laborious, expensive, and inefficient. The ICReDD tackles this issue by integrating the fields of computational science, information science, and experimental science. One of the key approaches to elucidate “unknown” reaction pathways is the automated reaction path search method termed “artificial force induced reaction (AFIR)” developed by the director Prof. Satoshi Maeda. The AFIR is a novel method used in quantum chemical calculations that applies virtual mechanical forces to reaction systems in search of potential pathways. Calculations can be optimized for complex systems by collaborating with information scientists, and predicted pathways can be tested with experimental scientists. Such interdisciplinary studies are expected to advance current understandings of reaction pathways and networks, and lead to the development of highly efficient chemical reactions and the innovative products.

The goal of Tanaka group is to create new fusion research fields and apply the results to medical fields, by combining computational science, information science, and experimental science. Specifically, we will create a new academic field designated as ‘material genomics’ that controls cell genomes using high-performance hydrogels developed in the ICReDD, and apply the results to cancer diagnosis/therapy, regenerative medicine, and discovery of therapeutic drugs. Finally, our sincere hope is that our ICReDD may contribute to a brighter and more prosperous future for all of humanity.

Keywords: WPI, ICReDD, chemical reaction, novel medical technology
While we may rejoice at the advances in modern technology and the resources available to us, cancer continues to be humanity’s major threat. It is therefore imperative that medical researchers find a solution to the problem of cancer.

Although research is being carried out in every part of the world, no ultimate solution has been found, or is even in sight. This makes it of the greatest urgency that medical specialists, wherever they are working, should have the opportunity to meet each other and discuss methods to combat, or prevent, the diseases.

In 1979, Dr. Hiroshi Kobayashi, now Professor Emeritus of Hokkaido University, inspired by the academically liberal atmosphere of The Gordon Research Conferences, Santa Barbara, California, the USA, conceived the idea of the Sapporo Cancer Seminar (SCS) to provide greater opportunities for cancer researches to share their knowledge in a relaxed but academic atmosphere. His proposal was encouraged by Dr. Takashi Sugimura, now President Emeritus of the National Cancer Center, Tokyo, and supported by Dr. Takeo Yamazaki, then President of the Hokkaido Medical Association, Sapporo, Hokkaido, Japan.

The first SCS was held in Sapporo in 1981, and in 1983 the SCS established itself as a foundation, with the warm support of businesses, pharmaceutical organizations, and the general public. Since 1987, it has been a twice-yearly event, in February and July. The summer seminar deals with basic aspects of cancer research, while the winter seminar, which is scheduled to coincide with Sapporo’s Snow Festival, an internationally famous event, concentrates upon cancer-related clinical investigations.

The July seminar consists of symposia, a poster session with general discussions and meetings. Reports are published in Cancer Research and other world journals. The road to the conquering of cancer is likely to entail a long trek. The SCS aims to contribute its own small part to the advancement of medicine in its fight against this threat to human life.

**Main Projects**
The Sapporo Cancer Seminar should,
1) Host international conferences on cancer: international symposium in summer, national cancer seminars in winter
2) Establish connections with cancer-related institutions throughout the world, and act to collect and store academic information about cancer
3) Manage its affairs in an appropriate manner
4) Compile reports on the deliberations held at its symposia, and publish these in the appropriate journals

The first symposium on cancer held in the summer of 1981, its theme was Escape of Tumor Cells from Immune Controls.
## Brief History of Sapporo International Cancer Symposium

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Hokkaido University was selected for the World Top Level Research Center Program as WPI on October 4, 2018. WPI stands for World Premier International Research Center Initiative. In 2007, Japanese Ministry, MEXT started the WPI program for the establishment of the global brain circulation hub where talented young researchers gather from all over the world. The budget scale is approximately 70 million USD for 10 years which is the Japan's largest competitive research fund. Four pillars of WPI are 1) Science, implementing the world's highest level of research, 2) Fusion, generating fused research domains, 3) Globalization, creating international research environments, and 4) Reform, innovating research organizations.

Hokkaido University launched the institute for quantum chemistry as the Institute for Chemical Reaction Design and Discovery (ICReDD). Prof. Satoshi Maeda, director of this Institute, invented artificial force induced reaction (AFIR) method. When chemical substances A and B react and produce a final product AB, virtual artificial force excited both A and B on the computer through AFIR method, and then according to the chemical reaction along with the lowering energy direction, the final product AB is efficiently obtained. In Hokkaido Univ., Prof. Akira Suzuki repeatedly performed the experiments for many times to discover the Suzuki-Miyaura coupling method in 70’s (Nobel Prize for chemistry, 2010). The AFIR method can create a new chemical reaction by using the power of computational chemistry instead of repeated experiments. Actually, the AFIR method predicts the route of making amino acids from carbon dioxide, and this profession was proved after 10 years. The Harbor Bosch method is a ground-breaking invention referring as “making bread from air”, and AFIR should be the future version. In ICReDD, challenging projects by fusing computational science, information science, and experimental science are proceeded by 14 principal investigators (PIs). Prof. Gong who is the world-top leader of polymer chemistry produces original hydrogels, and the Medical application is one of the goals of these ICReDD projects. Although it is an unknown area that attempts to control living organisms using biomaterials created by optimal chemical reactions. The goal of Tanaka’s Lab is to create new methods for diagnosis and treatments of diseases.

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### Principal Investigators of WPI-ICReDD

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