Program

International Academy for Advanced Oncology

IAAO 2024

Innovative Initiatives for Challenging Treatments

2024 July 26 (Fri) 13:00 – 18:30
July 27 (Sat) 9:00 – 15:00
@ Toranomon Hills Forum

C-FINDs
CHUGAI FOUNDATION
FOR INNOVATIVE DRUG DISCOVERY SCIENCE

Innovative Initiatives for Challenging Treatments

DAY 1: Friday, July 26, 2024 13:00 – 18:30 On-site in Tokyo

Opening Remarks

13:00 **Motoo Ueno**, President, Chugai Foundation for Innovative Drug Discovery Science (C-FINDs)

1. Keynote Lecture

13:05 **One Drug is Not Enough**
Speaker: **Bruce A. Chabner, MD**, Professor, Harvard Medical School, USA
Chair: **Kiyohiko Hatake, MD, PhD**, Professor, Akasaka Sanno Medical Center, Japan

2. New Insights in Anti-Tumor Immunotherapy

13:25 **Personalized Cancer Vaccines: Encouraging Results and New Opportunities**
Speaker**: Catherine J. Wu, MD**, Professor, Harvard Medical School, USA
Chair: **Hiroyoshi Nishikawa, MD, PhD,** Professor, Nagoya University, Japan

14:05 **Spatial Organization of the Immune Response in Cancer**
Speaker: **Nir Hacohen, PhD**, Professor, Harvard Medical School, USA
Chair: **Hiroyoshi Nishikawa, MD, PhD,** Professor, Nagoya University, Japan

14:45 **Break**

3. Novel Treatment Strategies in Brain Tumor

15:00 **CAR T Cell Therapy for Glioblastoma: Clinical Insights for Response and Resistance**
Speaker: **Christine Brown, PhD**, Professor, City of Hope, USA
Chair: **Hitoshi Nakagama, MD, D.M.Sc,** President, National Cancer Center, Japan

15:40 **A Blood Test for Brain Tumors: How Microfluidics Can Enable Insight into Patient Response**
Speaker: **Shannon Stott, PhD**, Associate Professor, Harvard Medical School
Chair: **Hitoshi Nakagama, MD, D.M.Sc,** President, National Cancer Center, Japan

16:20 **Genetic Alterations and Cell-of-Origin in Medulloblastoma**
Speaker: **Hiromichi Suzuki, MD, PhD**, Chief, National Cancer Center, Japan
Chair: **Hitoshi Nakagama, MD, D.M.Sc,** President, National Cancer Center, Japan

17:00 **Break**

4. Innovative Research in Microbiome

17:10 **Host-Microbiome Interaction in Health and Disease**
Speaker: **Eran Elinav, MD, PhD**, Professor, Weizmann Institute of Science, Israel
Chair: **Naoko Ohtani, MD, PhD**, Professor, Osaka Metropolitan University, Japan

17:50 **Targeting the Microbiota for Cancer Immunotherapy**
Speaker: **Giorgio Trinchieri, MD**, Chief, National Cancer Institute, USA
Chair: **Naoko Ohtani, MD, PhD**, Professor, Osaka Metropolitan University, Japan

18:30 **Announcement (C-FINDs)**

19:00 **Networking Dinner**

Official language: English
Dress Code: Business Casual

DAY 2: Saturday, July 27, 2024 9:00 – 15:00 On-site in Tokyo

5. Keynote Lecture

9:00 **New Immunotherapy Approaches for Microsatellite Stable (MSS) Colorectal Cancer**
Speaker: **Josep Tabernero, MD, PhD**, Director, Vall d'Hebron Institute of Oncology, Spain
Chair: **Chikashi Ishioka, MD, PhD**, Director, JR Sendai Hospital, Japan

9:40 **Break**

6. Leverage of Real World Data in EU, US and Japan

9:55 **Clinical Cancer Genomics: Informing Real World Clinical Oncology and Driving Further Treatment Advances and Biological Insights**
Speaker: **Marc Ladanyi, MD,** Chief, Memorial Sloan Kettering Cancer Center, USA
Chair: **Hiroyuki Mano, MD, PhD,** Director, National Cancer Center Research Institute, Japan

10:35 **Leverage of Real World Data in France and EU**
Speaker: **Axelle Menu-Branthomme, MD,** Medical Expert, Health Data Hub, France
Chair: **Hiroyuki Mano, MD, PhD,** Director, National Cancer Center Research Institute, Japan

11:15 **Real-World Evidence Generated from C-CAT's Big Data**
Speaker: **Takashi Kohno, PhD,** Chief, National Cancer Center, Japan
Chair: **Hiroyuki Mano, MD, PhD,** Director, National Cancer Center Research Institute, Japan

11:55 **Lunch/ Advisory Board Meeting**

7. Breakthrough Technology Session: Protein Degrader, Precision Diagnosis, Efficacy Prediction

12:45 **Targeted Protein Degradation Approaches for Cancer Drug Discovery**
Speaker: **Zoran Rankovic, PhD,** Professor, The Institute of Cancer Research, UK
Chair: **Masakazu Toi, MD, PhD**, Director, Tokyo Metropolitan Komagome Hospital, Japan

13:25 **Multimodal and Generative AI for Pathology**
Speaker: **Faisal Mahmood, PhD,** Associate Professor, Harvard Medical School, USA
Chair: **Masakazu Toi, MD, PhD**, Director, Tokyo Metropolitan Komagome Hospital, Japan

14:05 **Liquid Biopsies for Cancer Detection and Characterization**
Speaker: **Maximilian Diehn, MD, PhD,** Professor, Stanford University, USA
Chair: **Masakazu Toi, MD, PhD**, Director, Tokyo Metropolitan Komagome Hospital, Japan

Closing Remarks

14:45 **Hiroyuki Mano, MD, PhD**, Director, National Cancer Center Research Institute, Japan

Next Forum Information

IAAO 2025

Date: Friday August 1 – Saturday August 2, 2025
Venue: Toranomon Hills Forum, Tokyo

Opening Remarks

Motoo Ueno

President, Chugai Foundation for Innovative Drug Discovery Science (C-FINDs)

As president of C-FINDs, I am very pleased to be able to hold the International Academy for Advanced Oncology onsite again this year. I would like to express my sincere gratitude to all of the distinguished guests, experts, and investigators attending this conference from overseas and Japan. C-FINDs has three guiding principles: "Top-level science", “Development of young researchers", and "Global perspective”. IAAO is a major C-FINDs event that reflects these three principles.

We are very pleased that, as ever, more than 250 people will be in attendance at this our fourteenth meeting, which is being held in a new location, Toranomon Hills Forum. We are always encouraged by the positive feedback that we receive from participants, and we are extremely happy and honored to know that more and more experts are interested in and value this event.

We are very fortunate to have in attendance so many world-class experts to share their experience, knowledge, and insights. I am confident this year’s forum will spark extensive and wide-ranging discussions. I encourage everyone to seize the opportunity provided by each session to actively engage in the discussions. Your comments and insights will be truly valuable to others attending this forum.

The theme of this year’s meeting is “Innovative Initiatives for Challenging Treatments”. The program focuses on cutting-edge research and the latest knowledge in the field of oncology from basic to applied science. We have thirteen great experts from overseas and two from Japan. This exceptional program was organized through the active discussions and hard work of the members of the IAAO Advisory Board: Dr. Chabner, Dr. Mano, Dr. Hatake, Dr. Ishioka, Dr. Kitagawa, Dr. Miyazono, Dr. Nakagama, Dr. Nishikawa, Dr. Ohtani, Dr. Tabernero, and Dr. Toi. I sincerely appreciate and respect the leadership and dedication of these eleven board members.

In closing, I would thank you again for participating onsite. C-FINDs’ sincere wish is that this two-day event will be a highly informative and fruitful time for everyone. Our ultimate goal is for the IAAO forum to become an important venue for the exchange of information that advances the fight against cancer and, concurrently, empowers patients to deal with their treatment proactively and with hope.

Thank you very much for your attention.

Session 1

Keynote Lecture

One Drug is Not Enough

Speaker: Bruce A. Chabner, MD (Professor, Harvard Medical School, USA)

IAAO2024

One Drug is Not Enough

Speaker

Bruce A. Chabner, MD

Professor of Medicine, Harvard Medical School, USA
Clinical Director, Emeritus, MGH Cancer Center,
Massachusetts General Hospital, USA

Chair

Kiyohiko Hatake, MD, PhD

Professor, Akasaka Sanno Medical Center, Japan

Bruce A. Chabner, MD

Research Summary

Dr. Chabner's major interest is in the clinical testing, pharmaco-kinetics, and biochemical pharmacology of new anticancer drugs, particularly natural products and signal transduction inhibitors.

Professional Experience/Awards

Dr. Chabner is the Clinical Director, Emeritus, of the Massachusetts General Hospital Cancer Center, and has had extensive experience in the field of cancer drug discovery and development. During his career at the National Cancer Institute (1971-1995), he served as a Senior Investigator in the Laboratory of Chemical Pharmacology, Chief of the Clinical Pharmacology Branch, Director of the Clinical Oncology Program, and Director of the Division of Cancer Treatment.

At the NCI, he maintained an active laboratory program in cancer pharmacology, and led the development of paclitaxel, fludarabine, and cisplatin, His research contributed significantly to the development of high dose chemotherapy regimens, and to standard therapies for lymphoma. In 1995, he became the first Clinical Director of the MGH Cancer Center and established a clinical trials and translational research effort that has identified multiple new target therapies for Non-Small cell Lung Cancer, Breast Cancer, and melanoma.

Dr. Chabner was for 27 years (1995-2020) the Editor in Chief of the journal, The Oncologist, and serves on the advisory boards for some of the industry's leading innovators in drug development. In 2006, Dr. Chabner received a presidential appointment to the National Cancer Advisory Board at the NCI and chaired the NCAB from 2010 to 2013.

He has received numerous awards, including Phi Beta Kappa, Alpha Omega Alpha, the Public Health Service's Distinguished Service Medal, the Karnofsky Award of the American Society for Clinical Oncology and the Bruce F. Cain Award for Drug Development of the American Association for Cancer Research. In 2006, he was the first recipient of the Bob Pinedo Award for Contributions to Improvement in the Care of Cancer Patients.

Education

BA 1961 Yale College, USA
MD 1965 Harvard Medical School, USA

Abstract of the lecture

Over the past decade this meeting of the IAAO has featured many stories of breakthrough drugs in the cancer field, from targeted small molecules to immune-based approaches. All of these have made a significant impact on survival of patients with once-refractory forms of cancer. As an example of that progress, 50 new chemical entities have received approval in the United States in the past five years (2019-2023), only one of these approvals for what had been the past standard class of drugs, a chemotherapeutic agent. We will hear about further work in the frontier of cancer therapeutics on this year's agenda: vaccines, protein degraders, and new brain tumor therapies.

While many new agents have earned an important place in improving therapy, most have won approval based on high response rates in relapsed or refractory patients, and none has proven curative as a single agent, with the possible exception of CAR-T treatments for lymphoma and leukemia. We would like to consider how drugs currently in development should be used in future treatment settings, taking into account the history of existing drug development, specifically the selection of appropriate combination treatments.

A final thought with relevance to this year's program is the importance of having the ability to assess the subclinical disease burden. We will have a discussion of the significance of and recent notable technological advances in this issue. On this year's agenda are several talks that reveal outstanding progress in early disease detection using ctDNA, RNA, radiopharmaceuticals, and exosomes. I look forward to a remarkable IAAO program and thank our sponsors from the Chugai Foundation for bringing this session together.

References

1. **Chabner BA**, Thompson BB, and Gehri J. Reinventing Chemotherapy. *The Oncologist* (in press).
2. Simon R. Review of Statistical Methods for Biomarker Drive Clinical Trials. *JCO Precis Oncol* 2019; 3: 1-9.
3. Duke ES, Fusco MJ, ... Kluetz P, Pazdur R. Highlights of FDA Oncology Approvals in 2022: Tissue-Agnostic Indications, Dosage Optimization, and Diversity in Drug Development. *Cancer Discov* 2022; 12: 2739-2746.
4. Parikh AR, Chee BH, ... Van Loon K, Atreya CE. Minimal Residual; Disease using a Plasma-Only Circulating Tumor DNA Assay to Predict Recurrence of Metastatic Colorectal Cancer Following Curative Intent Treatment. *Clin Cancer Res* 2024; doi 10.1158/1078-0432.CCR 23-3660.

Session 2

New Insights in Anti-Tumor Immunotherapy

2-1. Personalized Cancer Vaccines: Encouraging Results and New Opportunities

Speaker: Catherine J. Wu, MD (Professor, Harvard Medical School, USA)

2-2. Spatial Organization of the Immune Response in Cancer

Speaker: Nir Hacohen, PhD (Professor, Harvard Medical School, USA)

Personalized Cancer Vaccines: Encouraging Results and New Opportunities

Speaker

Catherine J. Wu, MD

Professor, Medicine, Harvard Medical School
Chief, Division of Stem Cell Transplantation and Cellular Therapies
Lavine Family Chair, Preventative Cancer Therapies,
Dana-Farber Cancer Institute, USA

Chair

Hiroyoshi Nishikawa, MD, PhD

Professor, Department of Immunology, Nagoya University Graduate School of Medicine, Japan
Chief, Division of Cancer Immunology, Research Institute/Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center, Japan

Catherine J. Wu, MD

Research summary

Dr. Wu's previous studies have focused on dissecting mechanisms of effective tumor immunity in patients who have demonstrated long-lasting clinically evident immunity following HSCT. Together, those studies indicate that productive anti-tumor immune responses are long-lived, directed against multiple epitopes, elicit both B and T cell responses, and in general, are specific for an individual patient. Her team is now completing an analysis of the activation state of leukemia-infiltrating T cells before and after allotransplantation for CML and CLL, which appear to be predictive of clinical response. Altogether, these insights have led me to undertake three general approaches to devise immunotherapy for CLL patients that is personalized and directed against antigens that are truly specific to that individual tumor.

Professional experience/Awards

Dr. Wu's seminal work on chronic lymphocytic leukemia (CLL) has been organized around two major themes. The first is understanding the genomic landscape of the disease at initial presentation and its evolution over time and in response to selective pressure imposed by therapy. This avenue of research has been marked by landmark papers in the New England Journal of Medicine, Cell, Cancer Cell and Nature. The other research theme relates to the interaction between CLL cells and the immune system. This interest has led

her team to develop strategies to predict from the genetic profiles of CLL cells which antigens are most likely to generate an immune response against the leukemia.

This work has culminated in ongoing clinical trials where genomic information is being used to design a personalized vaccine to test the impact on generation of an immune response and anti-tumor activity.

Dr. Wu is a recipient of the Claudia Adams Barr Award in Cancer Research, a Damon-Runyon Clinical Investigator Award, a Doris Duke Clinical Scientist Development Award, a Howard Hughes Early Career Physician-Scientist Award, and was elected to membership of the American Society of Clinical Investigation. She received research funding from the NIH, the American Association for Cancer Research, and the Leukemia and Lymphoma Society.

Education

BS	1988	Harvard University, USA
MD	1994	Stanford University, USA

Abstract of the lecture

Multiple lines of evidence have convincingly demonstrated tumor neoantigens as an important class of immunogenic tumor antigens, and have motivated the development of personalized cancer neoantigen targeting approaches. Neoantigens arise from amino acid changes encoded by somatic mutations in the tumor cell and have the potential to bind to and be presented by personal HLA molecules. As a field, we have now successfully moved beyond the first wave proof-of-concept studies that have demonstrated the safety, feasibility and high immunogenicity of these personalized vaccines. An imperative now is to address the challenges of discovering and optimizing the selection of antigens to target, the delivery approach, and extending this promising approach to a broader array of cancer settings.

References

1. Ott PA, Hu Z, ... Hacohen N, **Wu CJ**. An Immunogenic Personal Neoantigen Vaccine for Patients with Melanoma. *Nature* 2017; 547: 217-221.
2. Keskin DB, Anandappa AJ, ... **Wu CJ**, Reardon DA. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature* 2019; 565: 234-239.
3. Hu Z, Leet DE, ... **Wu CJ**, Ott PA. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. *Nature Medicine* 2021; 27: 515-525.
4. Sellars MC, **Wu CJ**, Fritsch E. Cancer vaccines: Building a bridge over trouble waters. *Cell* 2022; 185: 2770-2788.
5. Oliveira G, Stromhaug K, ... Keskin DB, **Wu CJ**. Phenotype, specificity and avidity of antitumor CD8+ T cells in melanoma. *Nature* 2021; 596: 119-125.

Spatial Organization of the Immune Response in Cancer

Nir Hacohen, PhD

Director, Center for Cancer Immunotherapy
Krantz Family Center for Cancer Research
Director, Center for Cell Circuits, Broad Institute of Harvard and MIT
David P. Ryan Endowed Chair in Cancer Research
Professor of Medicine, Harvard Medical School, USA

Speaker

Hiroyoshi Nishikawa, MD, PhD

Professor, Department of Immunology, Nagoya University Graduate School of Medicine, Japan
Chief, Division of Cancer Immunology, Research Institute/Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center, Japan

Chair

Nir Hacohen, PhD

Research summary

The Hacohen laboratory consists of immunologists, geneticists, biochemists, technologists, physicians and computational biologists working together to develop new and unbiased technologies and strategies to understand basic immune processes and immune-mediated diseases, with an emphasis on the innate immunity, tool development and personalized medicine.

Professional experience

Dr. Nir Hacohen has pioneered systems biology tools that generate comprehensive cellular and molecular models of immunological processes and enable personalized immunotherapies. In the area of cellular systems biology, he carried out genome-wide genetic screens in primary immune cells and identified many factors that underlie the sensing of pathogens by myeloid cells, including the discovery that STING is a proton channel, thus explaining its diverse effects on innate immunity. In the area of cell type discovery, he contributed to the Human Cell Atlas by discovering new immune cell types including human dendritic cell subsets and their progenitors as well as T cells and their differentiation states. He also uncovered cell states associated with disease in bacterial/viral sepsis, lupus nephritis, and cancer immunity. More recently, he found that effective immunotherapy is associated with spatially organized immune cell structures in

tumors. In the area of cancer vaccines, he created machine learning-based methods to predict cancer antigens, and developed the first personalized approach to immunotherapy using vaccines that target patient-specific tumor neoantigens. This led to clinical trials in melanoma and glioblastoma multiforme, demonstrating induction of tumor-specific T cells that kill malignant cells and are durable for many years. His lab is currently working on using systems-level technologies to understand mechanisms of human immune diseases and model them in mice, with the goal of catalyzing new therapeutic strategies.

Dr. Hacohen is an institute member and the director of the Center for Cell Circuits at the Broad Institute of MIT and Harvard. He is the director of the Center for Cancer Immunology at Massachusetts General Hospital, and the David P. Ryan Professor of Medicine at Harvard Medical School. Hacohen is a recipient of the NIH Director's Innovator Award, the MGH Scholars Award, and the Martin Prize. He completed his Ph.D. in biochemistry at Stanford, and was a fellow at the Whitehead Institute at MIT. Hacohen developed an international workshop (the Irving Cancer Immunology Symposium) for advancing the careers of young cancer immunologists. He also founded Neon Therapeutics, which is now part of BioNTech.

Education

PhD Stanford University, USA
AB Harvard University, USA

Abstract of the lecture

In tumors, immune cells organize into networks, including complex tertiary lymphoid structures (TLS) and immune hubs centered around the chemokines CXCL9/10/11 and CCL19. I will discuss our work in colon cancer, melanoma and lung cancer identifying immune cells and immune hubs associated with effective responses to immunotherapy such as PD-1 blockade. Our group recently found a spatially organized immune cell hub that is distinct from mature tertiary lymphoid structures. Thus hubs is enriched for stem-like TCF7+PD-1+CD8+ T cells, activated CCR7+LAMP3+ dendritic cells and CCL19+ fibroblasts as well as the chemokines that organize these cells. Within the stem-immunity hub, we find preferential interactions between CXCL10+ macrophages and TCF7−CD8+ T cells as well as between mature regulatory dendritic cells and TCF7+CD4+ and regulatory T cells. Based on these findings and our previously identified hub of activated T cells with CXCL10+ macrophages, I will propose a model for the spatial organization of the human immune response in cancer and its relevance to patient immunotherapy outcomes.

References

1. Chen JH, Nieman L, …Korsunsky I, **Hacohen N**. Human lung cancer harbors spatially organized stem-immunity hubs associated with response to immunotherapy. *Nat Immunol*. 2024; 25: 644-658
2. Pelka K, Hofree M, …**Hacohen N**. Spatially organized multicellular immune hubs in human colorectal cancer. *Cell* 2021; 184: 4734-4752
3. Sade-Feldman M, Yizhak K, …Getz G, **Hacohen N**. Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. *Cell* 2018; 175: 998-1013

Session 3

Novel Treatment Strategies in Brain Tumor

3-1. CAR T Cell Therapy for Glioblastoma: Clinical Insights for Response and Resistance

Speaker: Christine Brown, PhD (Professor, City of Hope, USA)

3-2. A Blood Test for Brain Tumors: How Microfluidics Can Enable Insight into Patient Response

Speaker: Shannon Stott, PhD (Associate Professor, Harvard Medical School)

3-3. Genetic Alterations and Cell-of-Origin in Medulloblastoma

Speaker: Hiromichi Suzuki, MD, PhD (Chief, National Cancer Center, Japan)

CAR T Cell Therapy for Glioblastoma: Clinical Insights for Response and Resistance

Speaker

Christine Brown, PhD

Deputy Director, T Cell Therapeutics Research Laboratories
Heritage Provider Network Professor, Departments of Hematology & Hematopoietic Cell Transplantation and Immuno-Oncology, City of Hope, USA

Chair

Hitoshi Nakagama, MD, D.M.Sc

President, National Cancer Center, Japan

Christine Brown, PhD

Research summary

Dr. Brown's research is focused on developing and translating chimeric antigen receptor (CAR) T cell therapy for the treatment of solid tumors, with an emphasis on malignant brain tumors. Her laboratory's groundbreaking discoveries in the design of novel CARs, optimization of T cell manufacturing processes, utility of locoregional delivery and development of strategies to overcome the suppressive tumor microenvironment are advancing the application of CAR T cell therapy. These preclinical studies have led to the initiation of several first-in-human clinical trials, including clinical testing of IL13Rα2-, HER2- and CLTX-directed CAR T cell therapy for the treatment of glioblastoma and other malignant brain tumors. Dr. Brown's ongoing research efforts aim to develop next-generation strategies to limit tumor antigen escape and to overcome the suppressive tumor microenvironment, critical challenges limiting the effectiveness of CAR T cell therapy in solid tumors.

Professional Experience/Awards

Dr. Brown received her doctoral degree from the University of California, Berkeley, and was a Leukemia & Lymphoma Scholar during her post-doctoral fellowship at Pennsylvania State University. Dr. Brown is currently the Heritage Provider Network

Professor in Immunotherapy at City of Hope and is internationally recognized for her groundbreaking studies in CAR T cell therapy and its application to brain tumors.

Dr. Brown's research has been published in Nature Medicine, New England Journal of Medicine, Science Translational Medicine, Cancer Discovery, Clinical Cancer Research and other notable journals, as well as featured by many news and magazine outlets including CNN health, National Public Radio (NPR), O Magazine and US News and World Report. Dr. Brown has received prestigious research funding from the NCI, CIRM, Parker Institute for Cancer Immunotherapy, Ivy Foundation, Norris Foundation, and Marcus Foundation. Dr. Brown has more than ten patents in the field of CAR T cell therapy and her discoveries have been foundational for the starting of two publicly traded biotechnology companies.

Dr. Brown is also the Deputy Director of the T Cell Therapeutics Research Laboratories (TCTRL) at City of Hope, where she provides scientific oversight for TCTRL translational programs, which are dedicated to accelerating the clinical testing of CAR T cell therapy. Over the past decade, she has led and built multi-disciplinary teams for CAR T cell GMP manufacturing, quality control release, patient correlative studies and regulatory protocol management.

Education

BS	1990	Santa Clara University, USA
PhD	1998	University of California Berkeley, USA

Abstract of the lecture

Glioblastoma (GBM) is the most aggressive primary brain cancer in adults and one of the most lethal of human cancers. Despite aggressive standard-of-care, including tumor resection, chemoradiation, and electric fields, these tumors unfailingly recur, and the 5-year survival rate remains at less than 10%. Chimeric antigen receptor (CAR) T cell therapy is being explored in early-stage clinical trials as a strategy to improve treatment outcomes for patients with GBM. CAR T cell therapy, however, faces multiple challenges in the treatment of GBM and other solid tumors, including tumor heterogeneity and the suppressive microenvironment. Here, I will present our phase I clinical experience evaluating CAR T cell therapies for the treatment of recurrent GBM, with a particular emphasis on our insights for determinants of therapeutic response and clinical failure.

We have recently published the largest clinical trial to evaluate CAR T cell therapy for the treatment of recurrent GBM, treating 58 evaluable patients with IL13Ra2-targeted CAR T cells (1). This study established the feasibility and safety for repetitive locoregional administration of CAR T cells and demonstrated that CAR T cell therapy can mediate significant clinical benefit in a subset of patients (1, 2). Learnings from this and other on-going trials will be presented, which help inform biomarkers of therapeutic response and resistance. We have performed multi-omic correlative studies evaluating features of the pretreatment tumor by scRNAseq, CAR T cell persistence by multiparameter flow cytometry, and cytokine dynamics by multiplex ELISA. Importantly, these clinical data, along with supporting preclinical studies in syngeneic mouse models (3), highlight the dynamic interplay between CAR T cells and the patient's endogenous immune system as a determinant of response. We demonstrate that favorable clinical outcomes and CAR T cell bioactivity were associated with increased levels of intratumoral CD3+ T cells and elevated INFγ-related chemokines. Conversely, therapeutic failure was associated with high levels of extracellular matrix related genes, suppressive SPP1+ macrophages and the

immunosuppressive cytokine TGFβ. These findings are driving rationally designed next-generation approaches to improve CAR T cell therapy for the treatment of GBM.

References

1. **Brown CE**, Badie B, ... Forman SJ, Jensen MC. Bioactivity and Safety of IL13Rα2-Redirected Chimeric Antigen Receptor CD8+ T Cells in Patients with Recurrent Glioblastoma. *Clin Cancer Res* 2015; 21: 4062-72.
2. **Brown CE**, Alizadeh D, ... Forman SJ, Badie B. Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. *N Engl J Med* 2016; 375: 2561-9.
3. Alizadeh D, Wong RA, ... Forman SJ, **Brown CE**. IFNγ Is Critical for CAR T Cell–Mediated Myeloid Activation and Induction of Endogenous Immunity. *Cancer Discov* 2021; 11: 2248-65.

A Blood Test for Brain Tumors: How Microfluidics Can Enable Insight into Patient Response

Shannon Stott, PhD

Associate Professor of Medicine
Harvard Medical School, Massachusetts General Hospital Cancer Center, USA

Speaker

Hitoshi Nakagama, MD, D.M.Sc

President, National Cancer Center, Japan

Chair

Shannon Stott, PhD

Research summary

The Stott Laboratory comprises bioengineers and chemists focused on translating technological advances to relevant applications in clinical medicine. Specifically, her team is interested in using microfluidics and imaging technologies to create tools that increase understanding of cancer biology and of the metastatic process.

The Stott Laboratory is also focused on developing microfluidic technologies that can isolate tumor-specific extracellular vesicles from cancer patient plasma. Extracellular vesicles have been implicated in promoting tumor progression by manipulating the surrounding microenvironment.

Professional Experience/Awards

Dr. Stott is a Mechanical Engineer who has been working at the interface of technology, imaging and medicine. Dr. Stott has a broad background in microfluidics, optics, tissue engineering and cryopreservation, with a focus on their applications in clinical medicine and cell biology.

As a postdoctoral fellow in Mehmet Toner's laboratory, she co-invented the herringbone circulating tumor cell chip (HBCTC-Chip) a device that can successfully capture cancer

cells circulating in the blood stream of localized and metastatic cancer patients. This technology has been used to explore the biology of these extremely rare cells, identifying novel pathways for metastasis and bringing us a small step closer to understanding how cancer spreads and kills. Recently, this device has been scaled for large scale production, enabling the distribution of the HBCTC-Chip to multiple cancer centers across the country.

Additionally, Dr. Stott is an expert in high speed video microscopy, an imaging technique that has enabled the exploration of novel fluidic flow inside microfluidic devices and biological processes that occur at a micro-second time scale.

Dr. Stott has authored over 60 publications and cited over 25,000 times. She holds leadership positions on multiple academic and industrial boards and has had her work featured in multiple venues, from MIT Technology Review to the television show Jeopardy. In 2014, she received the American Cancer Society's Women Leading the Way to Wellness Award. In 2023, she received a Krantz Spark Award.

Education

BS	1997	Mechanical Engineering, University of New Hampshire, USA
MS	1999	Mechanical Engineering, University of Illinois, Urbana-Champaign, USA
PhD	2006	Mechanical Engineering, Georgia Tech, USA

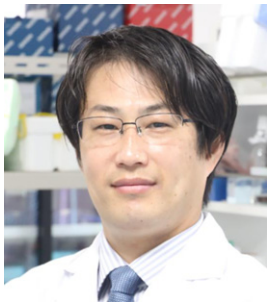
Abstract of the lecture

Advances in microfluidic technologies and downstream molecular assays have propelled the rapid growth in blood-based tests for cancer. While there is great interest in circulating tumor DNA for many solid tumors, the frequency of this DNA is limited for one of the most deadly forms of cancer, glioblastoma. For this reason we have taken a collaborative effort between bioengineers, biologists, and clinicians, to develop microfluidic devices that can isolate and characterize rare circulating tumor cells from the blood of brain tumor patients. As we have expanded our knowledge of these rare cells in circulation, we have worked to include other circulating biomarkers into our assay, including tumor-derived extracellular vesicles. Data from these devices will be presented, including the frequency at which we find them, how their number and phenotype change throughout treatment, and our work with paediatric patients. Transcriptomic and protein based signatures have been identified that suggest potential utility in the clinic to guide patient care. New technologies will also be shared, as we work to interrogate other patient biofluids, while also exploring how to align these results with other clinical data points such as MRI images. Through the microfluidic isolation of circulating biomarkers, our goal is to obtain complementary data to the current standard of care to help better guide treatment and identify new biomarkers and putative therapeutic targets.

References

1. Reátegui E^, van der Vos KE^, Lai CP^, ... Breakefield XO, **Stott SL**. Engineered nanointerfaces for microfluidic isolation and molecular profiling of tumor-specific extracellular vesicles. *Nat Commun* 2018; 9: 175. ^*Equal contribution*
2. Zachariah M, Oliveira-Costa JP, Carter B, **Stott SL***, Nahed BV*. Blood-Based Biomarkers for the Diagnosis and Monitoring of Gliomas. *Neuro Oncol* 2018; 20: 1155-1161. **co-corresponding*
3. Rabe DC, Ho U, … Flynn E, **Stott SL**. Aryl-diazonium salts offer a rapid and cost-efficient method to functionalize plastic microfluidic devices for increased immunoaffinity capture. *Adv Mater Technol* 2023; 8: 2300210.

Genetic Alterations and Cell-of-Origin in Medulloblastoma



Speaker

Hiromichi Suzuki, MD, PhD

Chief, Division of Brain Tumor Translational Research,
National Cancer Center, Japan

Chair

Hitoshi Nakagama, MD, D.M.Sc

President, National Cancer Center, Japan

Hiromichi Suzuki, MD, PhD

Research summary

Dr. Suzuki's team are working on the sequencing analysis of brain tumors to lead to the development of novel therapies.

Glioma is the most common type of malignant brain tumor in adults. Dr. Suzuki's team analyzed 757 cases with Grade II and III glioma and revealed the mutational landscape (H Suzuki et al., Nature Genetics. 2015). Their work contributed to the revised WHO classification in 2016 where the molecular diagnosis is employed.

Medulloblastoma is the most common malignant brain tumor in the paediatric population. Dr. Suzuki's team found a novel mutation of the non-coding gene, U1 small nuclear RNA (U1 snRNA) (H Suzuki et al., *Nature* 2019). The U1 snRNA is the most frequently mutated gene in medulloblastoma and has the potential to develop a novel therapeutic strategy.

Professional Experience/Awards

2005 – 2010	Resident in Neurosurgery, Toyohashi Municipal Hospital, Aichi, Japan
2014 – 2016	Post-doctoral research fellow, Pathology and Tumor biology, Kyoto
2016 – 2021	Post-doctoral research fellow, Developmental & Stem Cell Biology, Hospital for Sick Children, Toronto, Canada

2021 – Chief (Principal investigator), Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan
2023 JCA-Mauvernay Award (Japanese Cancer Association and Debiopharm)
2020 The Japan Neurosurgery Society Incitement and Special Award (The Japan Neurosurgery Society)
2019 GALLIE DAY 2019, 1st prize (Department of Surgery, University of Toronto)
2019 The Japanese Association of Medical Sciences Incitement Award (The Japanese Association of Medical Sciences)
2016 Japanese Cancer Association Incitement Award (Japanese Cancer Association)
2016 The Japan Neurosurgery Society Incitement Award (The Japan Neurosurgery Society)
2015 Hoshino Award (Japan Society of Neuro-Oncology)

Education

MD 2005 Nagoya University, Japan
PhD 2015 Nagoya University, Japan

Abstract of the lecture

Medulloblastoma is the most common malignant pediatric brain tumor. Based on gene expression or DNA methylation, medulloblastoma is classified into four subgroups: WNT, SHH, Group 3, and Group 4 with distinct molecular and clinical features. However, genomic alterations in medulloblastoma have not been fully elucidated. Therefore, little is yet known about its detailed pathogenesis.
Recently, large-scale genomic studies have identified novel genetic alterations in medulloblastoma. Notably, mutations in U1 small nuclear RNA (snRNA) and ELP1 gene have been predominantly detected in the SHH subgroup, revealing the important roles of abnormalities of RNAs in the pathogenesis of medulloblastoma. The development of single-cell RNA sequencing technology enables us to obtain a fine view of cell-level expression and analyze the cell-of-origin of cancers. With the comparison with normal human brain development, each medulloblastoma subgroup is specifically associated with distinct stages of neural progenitor cells. Furthermore, the discovery of mutations in the core binding factor alpha (CBFA) complex demonstrated that Group 3 and Group 4, of which tumorigenesis was unknown, arise due to the disruption of normal neural differentiation in the progenitor cell in rhombic lip subventricular zone caused by genetic alterations specific to the degree of the differentiation of cell-of-origin.
It has become evident that specific genetic abnormalities in the cells of origin lead to differentiation anomalies and tumorigenesis in medulloblastoma. The significant advances in understanding the pathogenesis of medulloblastoma would lead to the development of novel therapeutic strategies.

References

1. Vladoiu MC, El-Hamamy I, ...**Suzuki H**, ... Stein L. Taylor MD. Childhood cerebellar tumours mirror conserved fetal transcriptional programs. *Nature* 2019; 572: 67-73.
2. **Suzuki H**, Kumar SA, ... Stein L, Taylor MD. Recurrent non-coding U1-snRNA mutations drive cryptic splicing in Shh medulloblastoma. *Nature* 2019; 574: 707-711.
3. Shuai S, **Suzuki H**, ... Campo E, Stein LD. The U1 spliceosomal RNA is recurrently mutated in multiple cancers. *Nature* 2019; 574: 712-716.
4. Skowron P, Farooq H, ... **Suzuki H**, Taylor MD. The transcriptional landscape of Shh medulloblastoma. *Nat Commun* 2021; 12: 1749.
5. Hendrikse LD, Haldipur P, ...**Suzuki H**, Millen KJ. Failure of human rhombic lip differentiation underlies medulloblastoma formation. *Nature* 2022; 609: 1021-1028.

Session 4

Innovative Research in Microbiome

4-1. Host-Microbiome Interaction in Health and Disease

Speaker: Eran Elinav, MD, PhD (Professor, Weizmann Institute of Science, Israel)

4-2. Targeting the Microbiota for Cancer Immunotherapy

Speaker: Giorgio Trinchieri, MD (Chief, National Cancer Institute, USA)

IAAO2024

Host-Microbiome Interaction in Health and Disease

Eran Elinav, MD, PhD

Professor, Head, Systems Immunology Department, Weizmann Institute of Science, Rehovot, Israel
Professor, Division of Microbiome & Cancer, National German Cancer Research Center (DKFZ), Heidelberg, Germany

Speaker

Naoko Ohtani, MD, PhD

Professor, Department of Pathophysiology, Osaka Metropolitan University Graduate School of Medicine, Japan

Chair

Eran Elinav, MD, PhD

Research summary

For over a century immunology and microbiology focused on pathogens and how to eliminate them, which resulted in the discovery of antibiotics and vaccines. The last two decades marked the advent of microbiome research, as scientists realized that trillions of commensal microorganisms contribute to almost every aspect of human physiology. Bacteria, viruses, fungi and even parasites can modulate metabolic and inflammatory processes in the gut and extra-intestinal organs in various ways, and thereby give rise to or prevent diseases.

Professional Experience/Awards

Dr. Elinav is a professor heading the Department of Systems Immunology, Weizmann Institute of Science, Israel, and the director of the Microbiome & Cancer division, National German Cancer Center (Deutsches Krebsforschungszentrum, DKFZ), Heidelberg, Germany. His labs at the Weizmann Institute and DKFZ focus on deciphering the molecular basis of host-microbiome interactions and their effects on health and disease, with a goal of personalizing medicine and nutrition. Dr. Elinav completed his medical doctor's (MD) degree at the Hebrew University of Jerusalem Hadassah Medical Center summa cum laude, followed by a clinical internship, residency in internal medicine, and a physician-scientist position at the Tel Aviv Medical Center Gastroenterology institute. He received a

PhD in immunology from the Weizmann Institute of Science, followed by a postdoctoral fellowship at Yale University School of Medicine.

Dr. Elinav has published more than 250 publications in leading peer-reviewed journals, including major recent discoveries related to the effects of host genetics, innate immune function and environmental factors, such as dietary composition and timing, on the intestinal microbiome and its propensity to drive multi-factorial disease. His honors include multiple awards for academic excellence including the Claire and Emmanuel G. Rosenblatt award from the American Physicians for Medicine, the Alon Foundation award, the Rappaport prize for biomedical research, the Levinson award for basic science research, the Landau prize. He is an honorary guest professor, University of Science & Technology of China; a senior fellow at the Canadian Institute For Advanced Research (CIFAR); an elected member, European Molecular Biology Organization (EMBO); an elected fellow, American Academy of Microbiology; and an international scholar at the Howard Hughes Medical Institute (HHMI) and the Bill & Melinda Gates Foundation.

Education

MD	1999	Hebrew University of Jerusalem Hadassah Medical Center, Israel
PhD	2009	Weizmann Institute of Science, Israel

Abstract of the lecture

The mammalian intestine contains trillions of microbes, a community that is dominated by members of the domain Bacteria but also includes members of Archaea, Eukarya, and viruses. The vast repertoire of this microbiome functions in ways that benefit the host. The mucosal immune system co-evolves with the microbiota beginning at birth, acquiring the capacity to tolerate components of the community while maintaining the capacity to respond to invading pathogens. The gut microbiota is shaped and regulated by multiple factors including our genomic composition, the local intestinal niche and multiple environmental factors including our nutritional repertoire and bio-geographical location. Moreover, it has been recently highlighted that dysregulation of these genetic or environmental factors leads to aberrant host-microbiome interactions, ultimately predisposing to pathologies ranging from chronic inflammation, obesity, the metabolic syndrome and even cancer. We have identified various possible mechanisms participating in the reciprocal regulation between the host and the intestinal microbial ecosystem, and demonstrate that disruption of these factors, in mice and humans, lead to dysbiosis and susceptibility to common multi-factorial disease. Understanding the molecular basis of host-microbiome interactions may lead to development of new microbiome-targeting treatments.

References

1. Nobs SP, Kolodziejczyk AA, … Abdeen SK, **Elinav E**. Diabetic susceptibility to pulmonary viral infection is driven by an impaired metabolic-epigenetic lung dendritic cell function. *Nature* 2023; 624: 645-52.
2. Zheng D, Mohapatra G, … Abdeen SK, **Elinav E**. Epithelial Nlrp10 inflammasome mediates protection against intestinal auto-inflammation. *Nat Immunol* 2023; 24: 585-594
3. Stein-Thoeringer CK, Saini NY, … Jenq RR, **Elinav E**. A non-antibiotic-disrupted gut microbiome predicts clinical responses to CD19-targeted CAR-T cell immunotherapy across international cohorts. *Nat Med* 2023; 29: 906-916.
4. Fluhr L, Mor U, … Shapiro H, **Elinav E**. Gut microbiome modulates weight gain in mice after discontinued smoke exposure. *Nature* 2021; 600: 713-719.

Targeting the Microbiota for Cancer Immunotherapy

Speaker

Giorgio Trinchieri, MD

Chief, Laboratory of Integrative Cancer Immunology, National Cancer Institute, National Institutes of Health, USA

Chair

Naoko Ohtani, MD, PhD

Professor, Department of Pathophysiology, Osaka Metropolitan University Graduate School of Medicine, Japan

Giorgio Trinchieri, MD

Research summary

Dr. Trinchieri has contributed to the identification of the interplay between inflammation/innate resistance and adaptive immunity, and of the role of cytokines and interferons in the regulation of hematopoiesis, innate resistance and immunity in infections and cancer. His main focus now is the role of inflammation/innate resistance and commensal microbiota in carcinogenesis, cancer progression and therapy of cancer.

As Chief, Dr. Trinchieri oversees the operations of intramural laboratories that The Laboratory of Integrative Cancer Immunology (LICI) studies the role of the immune system in carcinogenesis, cancer associated morbidity and response to cancer therapy with a focus on the interactions between innate and adaptive resistance. Researchers in the LICI are developing interdisciplinary approaches combining novel biological, molecular and computational experimental approaches, bioinformatics, genetics, mathematical modeling and transkingdom network analysis to understand the complexities of immune and inflammatory processes and the role of pathogens and commensal microbes in the disease process of cancer, and translate this knowledge into progress in clinical care.

Professional Experience/Awards

Dr. Giorgio Trinchieri is an NIH distinguished investigator at the National Cancer Institute, National Institutes of Health. Previously, he has occupied research and administrative positions at the University of Torino, the Basel Institute of Immunology, the Swiss Institute for Experimental Cancer Research, the Wistar Institute, the University of Pennsylvania, and the Schering Plough company.

Dr. Trinchieri has advanced our understanding of the relationship between the innate and adaptive immune systems, and discovered interleukin-12 (IL-12), which helps enhance the immune system's ability to respond to cancer. This last achievement earned him the 1996 William B. Coley Award for Distinguished Research in Basic and Tumor Immunology, and his main focus now is on interplay between innate inflammation, the body's bacteria, and cancer. Dr. Trinchieri is an elected fellow of the National Academy of Sciences, the American Academy of Microbiology, and the Academy of Immuno-Oncology

Education

MD 1973 Universita, Di Torino, Italy

Abstract of the lecture

Growing evidence suggests that the gut microbiota modulates the efficacy and toxicity of cancer therapy, most notably immunotherapy and its immune-related adverse effects1, 2. The impaired response to immunotherapy in patients treated with antibiotics supports this role of the microbiota. Until recently, results pertaining to the identification of the microbial species responsible for these effects were incongruent, and relatively few studies analyzed the underlying mechanisms. Gut microbial communities (microbiotypes) with non-uniform geographic distribution were associated with favorable and unfavorable outcomes, contributing to discrepancies between cohorts3. Now, a better understanding of the taxonomy of the species involved and of their mechanisms of action has been achieved. Defined bacterial species have been shown to promote a response to immune checkpoint inhibitors through the production of different products or metabolites, although a suppressive effect of Gram(-) bacteria may be dominant in some unresponsive patients3. Machine learning approaches trained on patients' microbiota composition can predict the ability of patients to respond to immunotherapy with some accuracy3. Thus, the interest in modulating the microbiota composition to improve patients' responsiveness to therapy has been mounting. Our data of a fecal microbiota transfer clinical trial in anti-PD1 refractory melanoma patients has provided clinical proof of concept of the possibility to target the gut microbiota composition in cancer therapy4. Also, both in clinical studies and in experimental animals, diets rich in fibers improve the response to immunotherapy by modifying the gut microbiome suggesting the possibility of dietary approaches to target the microbiota composition in cancer therapy5. However, while many early clinical studies have analyzed the association of the microbiota composition with the response to anti-PD-1 in cancer patients, emerging evidence suggests that the association may be context dependent and different types of mono or combination immunotherapies may be differentially regulated by the microbiota, Thus, a more personalized approach depending original gut microbiota composition of the patients and the type of immunotherapy protocol selected may be necessary for optimal clinical results.

References

1. Dzutsev A, Badger JH, ... Smith CK, **Trinchieri G**. Microbes and Cancer. Annu Rev Immunol 2017; 35: 199-228.
2. Iida N, Dzutsev A, ... **Trinchieri G**, Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013; 342: 967-970.

3. McCulloch JA, Davar D, ... **Trinchieri G**, Dzutsev AK. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. *Nat Med* 2022; 28: 545-556.
4. Davar D, Dzutsev AK, ... **Trinchieri G**, Zarour HM. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 2021; 371: 595-602.
5. Spencer CN, McQuade JL, ... **Trinchieri G**, Daniel CR, Wargo J. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* 2021; 374: 1632-1640.

Session 5

Keynote Lecture

New Immunotherapy Approaches for Microsatellite Stable (MSS) Colorectal Cancer

Speaker: Josep Tabernero, MD, PhD
(Director, Vall d'Hebron Institute of Oncology, Spain)

IAAO2024

New Immunotherapy Strategies for Microsatellite Stable (MSS) Colorectal Cancer

Josep Tabernero, MD, PhD

Director, Vall d'Hebron Institute of Oncology (VHIO), Spain
Head of the Medical Oncology Department at the Vall d'Hebron University Hospital, Spain

Speaker

Chikashi Ishioka, MD, PhD

Director, JR Sendai Hospital, Japan
Professor Emeritus, Tohoku University, Japan

Chair

Josep Tabernero, MD, PhD

Research summary

Dr. Tabernero is active in phase I and II studies with pharmacodynamic endpoints with novel agents directed to cancer and immune cells' targets.
His laboratory is developing molecular therapies that target specific oncoproteins, with particular emphasis on EGFR-family, ERK, and PI3K-pathway inhibitors, for patients displaying genetic lesions or pathway dysregulation. The objectives of his laboratory include identifying new predictive markers of response to diverse treatments and studying circulating biomarkers (detection and genotyping of circulating free DNA). His group develops new xenograft models with explant tumors from patients ("xenopatients") in mice to study tumor development.

Professional experience

Dr. Tabernero serves on the Editorial Boards of various top tier journals including Annals of Oncology, ESMO Open, Cancer Discovery, Clinical Cancer Research, Cancer Treatment Reviews, and Nature Reviews Clinical Oncology. He has (co) authored approximately 600 peer-reviewed papers with an H-Index of 112.

He was the President (2018 – 2019) of the European Society for Medical Oncology´s (ESMO). He is also member of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO). He has also been a member of the Educational and Scientific Committees of ESMO, ECCO, ASCO, AACR, AACR/NCI/EORTC, ASCO Gastrointestinal, TAT and WCGIC meetings.

Dr. Tabernero has received many awards over the past two decades for his work. In 2017, he was selected as the 25th Medical Embassador of the Spanish Health, and in 2018 he received the Giants of Cancer Care Award in Gastrointestinal Cancer at the ASCO Annual Meeting.

Education

MD	1987	Universitat Autònoma de Barcelona, Spain
PhD	1987	Universitat Autònoma de Barcelona, Spain

Abstract of the lecture

Immunotherapy (IT) has been incorporated in the treatment of metastatic colorectal cancer (mCRC) with Microsatellite Instability High or Deficient Mismatch Repair system (MSI-H/dMMR) phenotype. Pembrolizumab and nivolumab (single agent or combined with ipilimumab) have demonstrated long-lasting responses ranging from 30% in pre-treated patients to 60% in the front-line setting. Molecular biology surrounding MSI-H/dMMR CRC favours IT response. Dysfunctional MMR system leaves unrepaired DNA alterations, mainly insertions and deletions in codons that modify the reading frame, resulting in Tumour Mutational Burden TMB over 10 mutations per megabase with high immunogenic potential. Further genomics, MSI-H/dMMR CRC is mainly clustered in Consensus Molecular Subtype 1 (CMS1), and associates immune infiltrates composed of different T cells subpopulations and cells belonging to innate immunity. However, this phenotype also exemplifies adaptive immune resistance through different mechanisms.
Since between 30-50% of MSI-H/dMMR mCRC do not benefit from IT, the better understanding of molecular traits associated with IT outcomes is an unmet need. Lynch syndrome diagnosis, PD-L1 expression and presence of BRAF/RAS mutations have been explored in trials but not correlated with IT response, although RAS mutant tumours benefited lesser than RAS wild-type in subgroup analysis of Keynote-177.
On the other hand, the efficacy of immune check-point inhibitors in MSS/pMMR CRC tumours is limited, especially in patients with liver metastasis. Several strategies are currently being developed to overcome this intrinsic resistance like the identification of potential biomarkers of response -beyond the MSI status, like POLE mutations and high TMB among others-, as well as new treatment approaches, like bi-specific antibodies, T-cell engagers and autologous vaccines, among others, with the main purpose of boosting immunogenicity. In this presentation, we will discuss these new therapeutic approaches in selected biomarker-defined populations.

Session 6

Leverage of Real World Data in EU, US and Japan

6-1. Clinical Cancer Genomics: Informing Real World Clinical Oncology and Driving Further Treatment Advances and Biological Insights

Speaker: Marc Ladanyi, MD (Chief, Memorial Sloan Kettering Cancer Center, USA)

6-2. Leverage of Real World Data in France and EU

Speaker: Axelle Menu-Branthomme, MD (Medical Expert, Health Data Hub, France)

6-3. Real-World Evidence Generated from C-CAT's Big Data

Speaker: Takashi Kohno, PhD (Chief, National Cancer Center, Japan)

Clinical Cancer Genomics: Informing Real World Clinical Oncology and Driving Further Treatment Advances and Biological Insights

Marc Ladanyi, MD

Chief, Molecular Diagnostics Service
William J. Ruane Chair in Molecular Oncology
Memorial Sloan Kettering Cancer Center, USA

Speaker

Hiroyuki Mano, MD, PhD

Director, National Cancer Center Research Institute, Japan

Chair

Marc Ladanyi, MD

Research Summary

The research program in Dr. Ladanyi's laboratory focuses on the genomics and molecular pathogenesis of sarcomas and thoracic malignancies, with an emphasis on clinical translation of potential diagnostic markers and therapeutic targets. Dr. Ladanyi also co-directs (with Chris Sander) the Genome Data Analysis Center at Memorial Sloan Kettering, which is part of the TCGA project network.

Professional Experience/Awards

Dr. Ladanyi is a molecular pathologist whose research laboratory studies the genomics and molecular pathogenesis of thoracic malignancies and select sarcomas, with an emphasis on genomic pathology/cancer genomics work on human cancer tissues and human cancer cell lines. The overall focus is on understanding pathobiology, improving molecular diagnosis, refining prognostication, and identifying new therapeutic targets. The approaches used include integrated genomics, functional genomic screens, chemical screens, and related single gene functional studies and pre-clinical studies. As part of his clinical responsibilities, he also leads the Molecular Diagnostics Service at MSKCC,

overseeing all clinical somatic and germline cancer genomic testing, including MSK-IMPACT and MSK-ACCESS testing.

Education

MD McGill University, Canada

Abstract of the lecture

The clinical cancer genomics testing program at MSKCC, centered on the MSK-IMPACT assay launched 10 years ago, anticipated what is now “real world” testing and its scale, now including genomic data on > 130,000 samples from >90,000 patients, is at the level of “real world” datasets. The presentation will highlight two overarching themes or threads: first, the “virtuous circle” of “bedside to bench to bedside” research enabled by clinical cancer genomic studies in patient cancer samples, and, secondly, the opportunity created by routine large scale genomic profiling to move beyond a single gene/single driver focus and mine the nonrandom, combinatorial aspects of the genomic landscape of human cancers both for its therapeutic opportunities and for biological insights into specific cancers. Clinical cancer genomics testing can identify potential novel therapeutic targets for preclinical validation, some of which are ultimately translated into the clinic, with cancer genomic studies of subsequent clinical samples shedding further light on determinants of response and mechanisms of drug resistance, which in turn guide further preclinical work to improve responses and ultimately patient outcomes, representing a “virtuous circle” (being the opposite of a “vicious circle”).

Leverage of Real World Data in France and EU

Axelle Menu-Branthomme, MD

Medical Expert, Health Data Hub, France

Speaker

Hiroyuki Mano, MD, PhD

Director, National Cancer Center Research Institute, Japan

Chair

Axelle Menu-Branthomme, MD

Short biography

Dr Menu-Branthomme is an experienced MD specialized in health informatics.
For more than 20 years, she has been committed to enhancing, sharing and facilitating access to health data for general interest projects in France.
She has coordinated numerous multilateral partnerships within the Greater Paris Hospital (AP-HP) and then on behalf of the French government (Technical agency for information on hospitalization (ATIH) and Regional health agency (ARS) of the Paris Region).
She has held the position of Medical Expert for the French Health Data Hub for over two years now.

Education

MD 1999 Université Paris Cité, France

Abstract of the lecture

Provided for by the 24 July 2019 Law on the organisation and transformation of the healthcare system, the French Health Data Hub (HDH) is a public structure whose objective is to enable project coordinators to easily access non-nominative data hosted on a secure platform, in compliance with regulations and citizens' rights. To achieve this, the HDH develops four main actions:

- Offering a one-stop shop to help project leaders with their administrative and regulatory procedures,
- Providing access to a catalogue of French health databases,
- Providing a secure, state-of-the-art platform with advanced data storage, calculation, reconciliation and analysis capabilities,
- Promoting the ecosystem to accelerate innovation by encouraging the sharing of experience and knowledge.

Launched in October 2022 and coordinated by the HDH, the HealthData@EU pilot brings together 17 major European stakeholders, including national health data platforms of several Member States (Finland, France, Norway, Denmark, Germany, Belgium, Hungary, Croatia and Spain), 2 European agencies (EMA and ECDC), and European research infrastructures (BBMRI, Elixir, eBRAINS). This project focuses on the creation of a first version of the HealthData@EU cross-border infrastructure planned in the draft regulation on the European Health Data Space (EHDS). This network will connect all the data-providing partners - data nodes - as well as the central services established at European Commission level. This technical infrastructure should enable the implementation of 2 priority services in the user journey (consulting metadata on a European portal; filling in a unified form to request access to health data).

Finally, the HDH is involved in other European initiatives, such as:
- mobilisation of a consortium of 19 French data managers to respond to the Direct Grant *Setting up services by Health Data Access Bodies* as part of the EU4Health program,
- construction of quality labels for health databases (call for projects *Developing a Data Quality and Utility Label for the EHDS*, supported by the European Commission; member of the QUANTUM European consortium supported by the Spanish institute IACS).

References

Health Data Hub. Paris 2024. Rapport annuel 2023. Le Health Data Hub publie son rapport annuel 2023 | Health Data Hub (health-data-hub.fr)

Real-World Evidence Generated from C-CAT's Big Data

Takashi Kohno, PhD

Director, Center for Cancer Genomics and Advanced Therapeutics,
Chief, Division of Genome Biology,
National Cancer Center, Japan

Speaker

Hiroyuki Mano, MD, PhD

Director, National Cancer Center Research Institute, Japan

Chair

Takashi Kohno, PhD

Research Summary

Dr. Takashi Kohno played a pivotal role in a significant clinical trial involving an *RET* fusion gene-targeting inhibitor, which he discovered in 2012. In 2021, insurance coverage for the RET inhibitor serpercatinib was achieved. Dr. Kohno's pursuits also include developing the NCC Oncopanel, a cancer gene panel test that gained insurance coverage in June 2019. His current activities focus on advancing cancer genomic medicine by utilizing gene panel test results for medical treatment and research and development.

Professional Experience/Awards

Dr. Kohno began his career as a Researcher in the Biology Division at the National Cancer Center Research Institute (NCCRI) from 1995 to 2000. He then advanced to become the Section Head of the Biology Division, serving from 2000 to 2010. Since 2011, he has been the Chief of the Division of Genome Biology at NCCRI. From 2018 to 2023, Dr. Kohno held the position of Section Head in the Section of Data Science Strategy at the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), NCC. In 2023, he was appointed Director of C-CAT.

Dr. Kohno has served on the Board of Directors since 2021 and has taken on the role of Vice-President for academic matters in basic research since 2023. He contributes to the academic community through his editorial roles. He is an Editor for Cancer Science and serves on the Editorial Boards of the Journal of Thoracic Oncology and Carcinogenesis.

His awards include the 2004 Japanese Cancer Association (JCA) Incentive Award, the 2018 JCA-CHAAO Award for *RET* fusion research, the 2020 Kobayashi Cancer Research Award, and the 2022 JCA-CHAAO Award for the development of the NCC Oncopanel.

Education

BS 1989 Kyoto University, Japan
PhD 1995 The University of Tokyo, Japan

Abstract of the lectura

Since June 2019, within the framework of the national health insurance system, Japan has commenced the implementation of cancer genomic medicine (CGM) through comprehensive genomic profiling (CGP). The Ministry of Health, Labour and Welfare (MHLW) of Japan has orchestrated a network of CGM facilities (comprising a total of 264 establishments as of May 1, 2024) and has established the C-CAT, serving as the central data repository for CGM. As of May 31, 2024, clinical data, including patient outcome data such as therapeutic response, therapeutic duration, and adverse events, and genomic data of 78,392 patients have been aggregated in C-CAT. The C-CAT data have presently been shared with around 100 groups, comprising CGM hospitals, academic institutions, and industries. The C-CAT big real-world data will be of great help for basic and clinical research as well as the planning of clinical trials. A recent comparative study with data from Whites within the AACR-GENIE database reveals frequent *TP53* mutations across various cancer categories as a characteristic of Asians. These activities will contribute to the generation of real-world evidence on advanced cancer patients in Asia.

References

1. **Kohno T**, Ichikawa H, … Yokota J, Shibata T. *KIF5B-RET* fusions in lung adenocarcinoma. *Nat Med* 2012; 18, 375-7.
2. Ogiwara H, Sasaki M, …Tominaga Y, **Kohno T**. Targeting p300 Addiction in CBP-Deficient Cancers Causes Synthetic Lethality by Apoptotic Cell Death due to Abrogation of MYC Expression, *Cancer Discov* 2016; 6: 430-45.
3. Ogiwara H, Takahashi K, … Okamoto A, **Kohno T**. Targeting the vulnerability of glutathione metabolism in ARID1A-deficient cancers. *Cancer Cell* 2019; 35: 177-190.e8.
4. Arakawa A, Ichikawa H, … **Kohno T**, Ogawa C*. Vaginal transmission of cancer from mothers with cervical cancer to infants. *N Engl J Med* 2021; 384: 42-50.
5. **Kohno T**, Kato M, … Yoshida T, Mano H. C-CAT: The National Datacenter for Cancer Genomic Medicine in Japan. *Cancer Discov* 2022; 12: 2509-2515.

Session 7

Breakthrough Technology Session: Protein Degrader, Precision Diagnosis, Efficacy Prediction

7-1. Targeted Protein Degradation Approaches for Cancer Drug Discovery

Speaker: Zoran Rankovic, PhD (Professor, The Institute of Cancer Research, UK)

7-2. Multimodal and Generative AI for Pathology

Speaker: Faisal Mahmood, PhD (Associate Professor, Harvard Medical School, USA)

7-3. Liquid Biopsies for Cancer Detection and Characterization

Speaker: Maximilian Diehn, MD, PhD (Professor, Stanford University, USA)

Targeted Protein Degradation Approaches for Cancer Drug Discovery

Zoran Rankovic, PhD

Professor of Chemical Biology, Director of the Centre for Protein Degradation, The Institute of Cancer Research, London, UK

Speaker

Masakazu Toi, MD, PhD

Director, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan

Chair

Zoran Rankovic, PhD

Research Summary

Dr. Rankovic is an expert in Targeted Protein Degradation, such as development of selective degraders of GSPT1 and CL1a proteins. The GSPT1 degrader has been recently out licensed for clinical development. Zoran's current research interests focus on expanding and leveraging targeted protein degradation approaches to study cancer biology and develop novel cancer treatments.

Professional Experience/Awards

Prior to joining the ICR, Zoran was Director of Chemistry at St. Jude Children's Research Hospital in Memphis, USA. There, Zoran instigated and directed development of a Targeted Protein Degradation program, which delivered several notable contributions, including the development of alternative cereblon warheads for the design of PROTACs with improved overall properties, and orally bioavailable potent and selective molecular glue degraders of GSPT1 and CK1a proteins.

Before joining St. Jude, Zoran was medicinal chemistry director and research fellow in Organon, Schering-Plough, Merck, and Eli Lilly. During his industrial career Zoran directed

teams that delivered multiple clinical candidates over a range of therapeutic areas including oncology, neurodegeneration, psychiatry, and cardiovascular disorders.

Zoran earned his PhD in organic chemistry from the University of Leeds, under the guidance of Professor Ronald Grigg. He serves on various scientific committees and advisory boards, including the NCI Chemical Biology Consortium for the Division of Experimental Therapeutics (NExT) Program, and is a co-lead of a cross-industry and academia Targeted Protein Degrader Safety Committee coordinated by the Health and Environmental Science Institute. Zoran authored and co-authored over 100 scientific publications, patents, book chapters, and edited two books on drug discovery topics.

Education

PhD 1995 University of Leeds, UK

Abstract of the lecture

Targeted protein degradation (TPD) is a rapidly emerging discovery paradigm that enables drugging currently intractable therapeutic targets and holds great promise for the development of breakthrough cancer therapies. The two distinct and currently most advanced TPD approaches, proteolysis targeting chimeras (PROTACs) and molecular glue degraders (MGDs), share the ubiquitin-proteasome system-dependent mechanism of action.

The immunomodulatory imide drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide are the first drugs identified to exert their pharmacological effect via the MGD mechanism. The IMiDs were found to bind to cereblon (CRBN), a substrate recognition domain of E3 ubiquitin ligase CRL4CRBN, which results in the recruitment and degradation of neosubstrates such as lymphoid transcription factors IKZF1 and IKZF3 that promote multiple myeloma proliferation.

A typical PROTAC consists of three distinct structural motifs: one binding to the protein of interest, another binding to an E3 ligase complex, and a linker tethering them together. Consequently, PROTACs tend to be large molecules (>700 kD), which can present considerable challenge in optimization of their physicochemical properties and development for clinical application. Owing to the small size and lead-like properties of IMiDs, the vast majority of PROTACs currently in the clinical development are CRBN-recruiting PROTACs.

This paper will discuss the general mechanism of actions of PROTACs and MGDs, and describe the development of potent, selective and orally bioavailable LCK-PROTAC, and GSPT1 and CK1α MGDs for the treatment of acute leukaemia.

References

1. Nishiguchi G, Mascibroda LG, … Klco JM, **Rankovic Z**. Selective CK1 Degraders Exert Antiproliferative Activity Against a Broad Range of Human Cancer Cell Lines. *Nature Commun.* 2024; 15: 482.
2. Nishiguchi G, Keramatnia F, … Fischer M, **Rankovic Z**. Identification of potent, selective and orally bioavailable small molecule GSPT1/2 degraders from a focused library of Cereblon modulators. *J Med Chem* 2021; 64: 7296-7311.
3. Alcock LJ, Chang Y, … Mullighan CG, **Rankovic Z**. Development of Potent and Selective Janus Kinase 2/3 Directing PG–PROTACs. *ACS Med Chem Lett* 2022; 13: 475-482.

4. Hu J, Jarusiewicz J, … **Rankovic Z**, Yang JJ. Preclinical evaluation of proteolytic targeting ofLCK as a therapeutic approach in T cell acutelymphoblastic leukemia. *Sci Transl Med* 2022; 14: eabo5228.
5. Min J, Mayasundari A, … Fischer M, **Rankovic Z**. Phenyl-Glutarimides: Alternative Cereblon Binders for the Design of PROTACs with Improved Chemical Stability and Degradation Efficiency. *Angew Chem Int Ed Engl* 2021; 60: 26663-266670.

Multimodal and Generative AI for Pathology

Faisal Mahmood, PhD

Associate Professor of Pathology at Harvard Medical School and the Division of Computational Pathology at the Brigham and Women's Hospital, USA

Speaker

Masakazu Toi, MD, PhD

Director, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan

Chair

Faisal Mahmood, PhD

Research Summary

Dr. Mahmood Lab at the Brigham and Women's Hospital aims to utilize machine learning, data fusion and medical image analysis to develop streamlined workflows for cancer diagnosis, prognosis and biomarker discovery. They are interested in developing automated and objective mechanisms for reducing interobserver and intraobserver variability in cancer diagnosis using artificial intelligence as an assistive tool for pathologists. The lab also focuses on the development of new algorithms and methods to identify clinically relevant morphologic phenotypes and biomarkers associated with response to specific therapeutic agents. They develop multimodal fusion algorithms for combining information from multiple imaging modalities, familial and patient histories and multi-omics data to make more precise diagnostic, prognostic and therapeutic determinations.

Professional Experience/Awards

After graduating from OIST in 2017, Dr. Mahmood conducted research on Deep Learning for Medical Image Analysis at the Johns Hopkins Whiting School of Engineering as a postdoctoral fellow:

- Histopathology Image Analysis: Developing fundamental tools for detection, segmentation and classification, domain adaptation in H&E and IHC images.
- Biomarker Discovery: Developing tools for understanding deep networks for identifying morphologic features and biomarkers of diagnostic and prognostic relevance as well as those with response to specific therapeutic agents.
- Endoscopy: Depth Estimation and 3D Topographical Reconstruction from the surface of the colon from monocular endoscopy images using Deep Learning. Fusing predicted depth into deep networks for improved polyp detection and classification.

He has been an associate member of the Broad Institute of MIT and Harvard since 2019. Starting in 2022, Dr. Mahmood is serving as an Associate Professor of Pathology at Harvard Medical School and the Division of Computational Pathology at the Brigham and Women's Hospital.

Education

PhD 2017 Okinawa Institute of Science and Technology (OIST), Japan

Abstract of the lecture

Advances in digital pathology and artificial intelligence have presented the potential to build assistive tools for objective diagnosis, prognosis and therapeutic-response and resistance prediction. In this talk we will discuss our work on: (1) Data-efficient methods for weakly-supervised whole slide classification with examples in cancer diagnosis and subtyping (Nature BME, 2021), identifying origins for cancers of unknown primary (Nature, 2021) and allograft rejection (Nature Medicine, 2022) (2) Discovering integrative histology-genomic prognostic markers via interpretable multimodal deep learning (Cancer Cell, 2022). (3) Building unimodal and multimodal foundation models for pathology, contrasting with language and genomics (Nature Medicine, 2024a, Nature Medicine 2024b). (4) Developing a universal multimodal generative co-pilot and chatbot for pathology (Nature, 2024). (5) 3D Computational Pathology (Cell, 2024) (6) Bias and fairness in computational pathology algorithms (Nature Medicine, 2024).

References

1. Lu MY, Chen B, ... Soliman A, **Mahmood F**. A Multimodal Generative AI Copilot for Human Pathology. *Nature* 2024 Jun 12. doi: 10.1038/s41586-024-07618-3.
2. Chen RJ, Ding T, ... Williams M, **Mahmood F**. Towards a general-purpose foundation model for computational pathology. *Nat Med* 2024; 30: 850-862.
3. Lu MY, Chen B, ... Parwani AV, **Mahmood F**. A visual-language foundation model for computational pathology. *Nat Med* 2024; 30: 863-874.
4. Chen RJ, Lu MY, ... Joo B, **Mahmood F**. Pan-cancer integrative histology-genomic analysis via multimodal deep learning. *Cancer Cell* 2022; 40: 865-878.
5. Lu MY, Chen TY, ... Lipkova J, **Mahmood F**. AI-based pathology predicts origins for cancers of unknown primary. *Nature* 2021; 594: 106-110.

Liquid Biopsies for Cancer Detection and Characterization

Maximilian Diehn, MD, PhD

Professor, Radiation Oncology, Stanford University, USA

Speaker

Masakazu Toi, MD, PhD

Director, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan

Chair

Maximilian Diehn, MD, PhD

Research Summary

Dr. Diehn's laboratory focuses on two main areas: 1) cancer stem cell biology and its implications for therapy and 2) development of genomics-based biomarkers for identifying the presence of malignant cells (diagnostic), predicting outcome (prognostic), and predicting response to therapy (predictive). Areas of study include cancers of the lung, breast, and gastrointestinal system. They are also interested in developing a deeper molecular understanding of normal and cancer stem cells, including identifying pathways and genes important for survival and self-renewal. Additionally, we are developing methods for overcoming resistance mechanisms to radiotherapy and chemotherapy in cancer stem cells. His laboratory members employ the tools of cancer genomics, including high throughput sequencing for detecting cancer mutations and quantifying gene expression. Clinically I specialize in the treatment of lung cancer and applications of stereotactic ablative radiotherapy and perform both prospective and retrospective clinical studies.

Professional Experience/Awards

Dr. Max Diehn received his bachelor's degree in biochemical sciences from Harvard College and his MD/PhD in biophysics from Stanford University. He is a board-certified radiation oncologist and specializes in the treatment of lung cancers.

Dr. Diehn's research program spans laboratory, translational, and clinical studies. His main areas of interest include liquid biopsies, lung cancer biology, and mechanisms of resistance to anti-cancer therapies including radiotherapy, immunotherapy, and targeted therapies. He has served on committees for a variety of national organizations including ASTRO, ASCO, AARC, and RSNA and is a Scientific Editor for Cancer Discovery.

Dr. Diehn has received funding from organizations such as the NIH, Department of Defense, and Stand Up To Cancer and he has been recognized with a variety of awards, including the NIH Director's New Innovator Award, the V Foundation Scholar Award, the Sidney Kimmel Scholar Award, the Doris Duke Clinical Scientist Development Award, and election into the American Society for Clinical Investigation.

In 2021, Dr. Diehn was elected to the National Academy of Medicine, which is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service

Education

MD	2004	Stanford University, USA
PhD	2004	Stanford University, USA

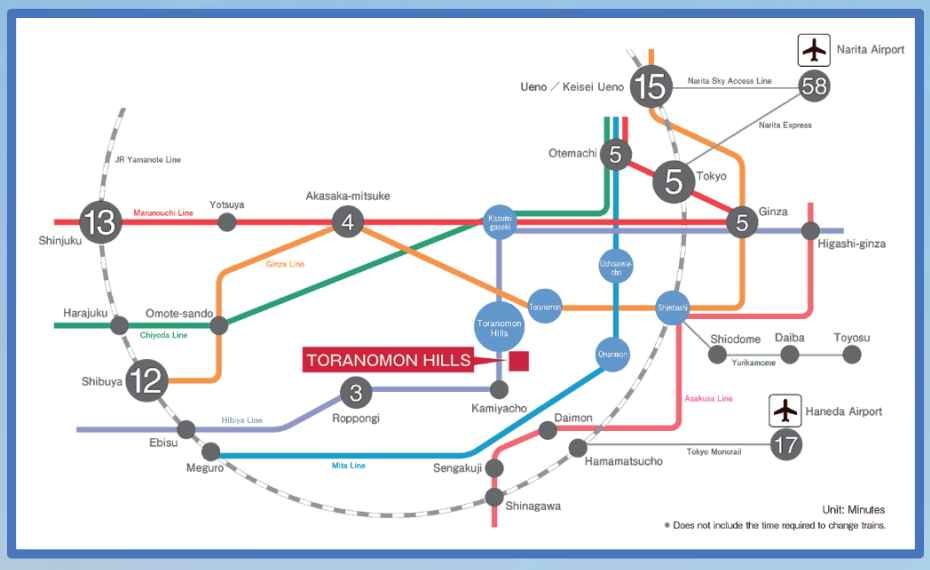
Abstract of the lecture

Circulating nucleic acids represent a promising biomarker for sensitive, specific, and dynamic detection of cancers. Additionally, emerging liquid biopsy methods that can measure more than just cancer-derived mutations enable non-invasive molecular characterization of cancers. In this presentation, I will focus on the use of circulating nucleic acid analysis to detect the presence of minute amounts of cancer cells and to molecularly characterize cancers. I will present data our group has generated using several novel liquid biopsy assays in order to highlight the broad range of information that can now be acquired using emerging approaches.

Access Map

Venue: Toranomon Hills Forum

5F, Toranomon Hills Mori Tower, 1 Chome-23-1 Toranomon,
Minato City, Tokyo 105-6390



11-minute walk from the Karasumoriguchi Exit of Shimbashi Stn.

Subway:
Hibiya Line
Toranomon Hills Stn
1. B1 Exit
2. A1b Exit

Ginza Line
Toranomon Stn
1. B1 Exit
2. B4 Exit

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