Program

International Academy for Advanced Oncology

IAAO 2023

Frontiers in Cancer Eradication: From Basic to Novel Approaches

2023 July 28 (Fri) 13:20 – 18:05
July 29 (Sat) 9:00 – 15:00
@ Roppongi-Academyhills 49

C-FINDs

CHUGAI FOUNDATION
FOR INNOVATIVE DRUG DISCOVERY SCIENCE

Frontiers in Cancer Eradication: From Basic to Novel Approaches

DAY 1: Friday, July 28, 2023 13:20 – 18:05 On-site in Tokyo

Opening Remarks

13:20 **Motoo Ueno**, President, Chugai Foundation for Innovative Drug Discovery Science (C-FINDs)

1. Keynote Lecture

13:25 **The Intersection of Chemotherapy and Immunotherapy: 5-Azacytidine**
Speaker: **Bruce A. Chabner, MD**, Professor, Harvard Medical School, USA
Chair/Moderator: **Kohei Miyazono, MD, PhD**, Distinguished Professor, The University of Tokyo, Japan

2. Progress in Antibody-Drug Conjugates

14:05 **Research and Development of Novel ADC Technology, DXd ADC**
Speaker**: Takashi Kagari, PhD**, Vice President, Discovery Research Laboratories I, Daiichi Sankyo Co., Ltd., Japan
Chair/Moderator: **Masakazu Toi, MD, PhD**, Director, Tokyo Metropolitan Komagome Hospital, Japan

14:45 **Biomarkers Predicting Response to Antibody Drug Conjugates: Should We Focus on the Target Antigens?**
Speaker: **Giuseppe Curigliano, MD, PhD**, Professor, University of Milan, Italy
Chair/Moderator: **Masakazu Toi, MD, PhD**, Director, Tokyo Metropolitan Komagome Hospital, Japan

15:25 **Break**

3. Molecular Targeting Therapy: Challenges in Control of the MAPK/ERK Pathway

15:45 **Mechanisms Driving Evolution of TKI-Resistance in Non-Small Cell Lung Cancer**
Speaker: **Aaron Hata, MD, PhD**, Assistant Professor, Medicine, Harvard Medical School, USA
Chair/Moderator: **Hiroyuki Mano, MD, PhD**, Director, National Cancer Center Research Institute, Japan

16:25 **Splicing Vulnerability in RAS Q61 Mutant Cancers**
Speaker: **Yoshihisa Kobayashi, MD, PhD**, Staff Scientist, Div. Molecular Pathology, National Cancer Center Research Institute, Japan
Chair/Moderator: **Hiroyuki Mano, MD, PhD**, Director, National Cancer Center Research Institute, Japan

17:05 **Break**

4. Special Session

17:25 **New Immunotherapy Approaches for Microsatellite Stable (MSS) Colorectal Cancer**
Speaker: **Josep Tabernero, MD, PhD**, Director, Vall d'Hebron Institute of Oncology, Spain
Chair/Moderator: **Yuko Kitagawa, MD, PhD**, Professor, Keio University, Japan

18:05 **Announcement (C-FINDs)**

18:25 **Networking Dinner**

Official language: English
Dress code: Business Casual

DAY 2: Saturday, July 29, 2023 9:00 – 15:00 On-site in Tokyo

5. Deepening the Understanding of Cancer and Immunity

9:00 **Integrating Systems Immunology with Metabolism and Cancer**
Speaker: **Hongbo Chi, PhD,** Professor, St. Jude Children's Research Hospital, USA
Chair/Moderator: **Hiroyoshi Nishikawa, MD, PhD**, Chief, Div. Cancer Immunology, National Cancer Center, Japan

9:40 **Gamma Delta T Cells Offer a Conserved Mechanism that Discriminates Cancer Cell Pathology from Healthy Cell Physiology**
Speaker: **Adrian Hayday, PhD,** Professor, King's College London, UK
Chair/Moderator: **Hiroyoshi Nishikawa, MD, PhD**, Chief, Div. Cancer Immunology, National Cancer Center, Japan

10:20 **Break**

6. Cancer Genomics & Biology: Basics & Applications

10:35 **Evolutionary Histories of Breast Cancer and Related Clones**
Speaker: **Seishi Ogawa, MD, PhD,** Professor, Kyoto University, Japan
Chair/Moderator: **Chikashi Ishioka, MD, PhD**, Professor, Tohoku University, Japan

11:15 **WNK1 Signaling Regulates Amino Acid Transport and mTORC1 Activity to Sustain AML Growth**
Speaker: **Kristian Helin, PhD,** Professor, The Institute of Cancer Research, London, UK
Chair/Moderator: **Chikashi Ishioka, MD, PhD**, Professor, Tohoku University, Japan

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

7. Breakthrough Technology 1: Single Cell Analysis

12:50 **Dissecting Human Gliomas by Single-Cell Genomics**
Speaker: **Mario L. Suvà, MD, PhD,** Associate Professor, Pathology, Harvard Medical School, USA
Chair/Moderator: **Hitoshi Nakagama, MD, PhD**, President, National Cancer Center, Japan

8. Breakthrough Technology 2: Application of CAR-T

13:30 **CAR-T Cell Therapies in Solid Tumors – BNT211 Targeting CLDN6 in Combination with an RNA Vaccine and Beyond**
Speaker: **Benjamin Rengstl, MD, PhD,** Director, Immunoreceptor Therapy, BioNTech SE, Germany
Chair/Moderator: **Kiyohiko Hatake, MD, PhD**, Professor, Akasaka Sanno Medical Center, Japan

14:10 **Drivers in CAR-T Cell Therapy**
Speaker: **Marcela V. Maus, MD, PhD,** Assistant Professor, Medicine, Harvard Medical School, USA
Chair/Moderator: **Kiyohiko Hatake, MD, PhD**, Professor, Akasaka Sanno Medical Center, Japan

Closing Remarks

14:50 **Hiroyuki Mano, MD, PhD**, Director, National Cancer Center Research Institute, Japan

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 (IAAO) onsite for the first time in 4 years. I would like to express my sincere gratitude to all of the distinguished guests, experts, and investigators attending this conference from overseas and Japan.

More than a year has passed since the foundation changed its name to C-FINDs. I believe that everyone here has heard the name C-FINDS by now. C-FINDs has three guiding principles: "Top-level science", “Development of young researchers", and "Global perspective”. IAAO is one of the most important activities of C-FINDs that reflects these three principles.

This year, our thirteenth meeting, is no exception as more than 250 people will be in attendance. 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 who 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 “*Frontiers in Cancer Eradication: From Basic to Novel Approaches*”. The program focuses on cutting-edge research and the latest knowledge in the field of oncology from basic to applied science. We have twelve great experts from overseas and three from Japan. First, we will hear from Dr. Chabner, the global leader of the IAAO advisory board, in his keynote lecture on a new path to cancer treatment. Then, we will have seven valuable sessions as described in the program.

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. Rosen, Dr.

Tabernero, and Dr. Toi. I sincerely appreciate and respect the leadership and dedication of these eleven board members.

In closing, allow me to once again thank you for participating onsite this year. 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

The Intersection of Chemotherapy and Immunotherapy: 5-Azacytidine

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

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Title: The Intersection of Chemotherapy and Immunotherapy: 5-Azacytidine

Speaker

Bruce A. Chabner, MD

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

Chair/Moderator

Kohei Miyazono, MD, PhD

Distinguished Professor, Graduate School of Medicine, The University of Tokyo, 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

As the field of oncology moves at breathtaking pace beyond chemotherapy into immunotherapy and molecularly adapted cell-based therapies, it is worthwhile to reflect on the preserved and even expanded role of chemotherapy as an adjunct to the newer treatment modalities. The unusual story of 5-aza cytidine and its closely related decitabine teaches us that simple and straightforward analogues may have important biological activities not initially appreciates at their entry into clinical trials. 5-aza cytidine entered the clinic more than 5 decades ago as a traditional cytotoxic agent, a cytidine analogue and inhibitor of DNA synthesis but failed to exhibit useful antileukemic activity at maximally tolerated doses. It had modest antileukemic effects that were countered by significant toxicities. The subsequent discovery of its target, DNA methyl transferase 1, and its ability to demethylate promoter regions of key differentiation pathways led to is effective use in low doses against myelodysplastic syndromes. Most recently, its enhancement of T-cell and NK cell antitumor activity, and tumor antigen expression, and evidence of significant activity against peripheral T-cell neoplasms, have opened additional avenues of clinical translational study for this unique class of drugs as enhancers of immunotherapy and particularly CAR-T regimens. The actual mechanisms of this immune enhancement on a molecular level will require further definition. One current theory is that the drug promotes expression of endogenous retroviral elements, which in turn stimulates a broad immunological response. The lesson from this experience is that a clear understanding of the biological effects of drugs can lead to important new applications and even new concepts in cancer treatment. Without a doubt, this intersection of biological effects of chemotherapy and immunity is not unique and deserves renewed attention in view of the expanding clinical use of these two modalities together.

Session 2

Progress in Antibody-Drug Conjugates

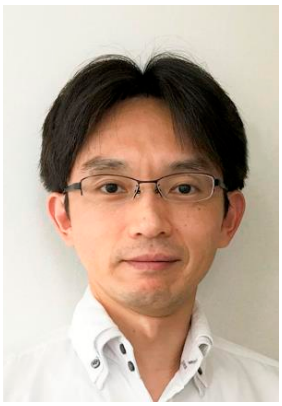
2-1. Research and Development of Novel ADC Technology, DXd ADC

Speaker: Takashi Kagari, PhD
(Vice President, Discovery Research Laboratories I, Daiichi Sankyo Co., Ltd., Japan)

2-2. Biomarkers Predicting Response to Antibody Drug Conjugates: Should We Focus on the Target Antigens?

Speaker: Giuseppe Curigliano, MD, PhD
(Professor, University of Milan, Italy)

Title: Research and Development of Novel ADC Technology, DXd ADC



Speaker

Takashi Kagari, PhD

Vice President, Discovery Research Laboratories I,
Research Function, R&D Division,
Daiichi Sankyo Co., Ltd., Japan

Chair/Moderator

Masakazu Toi, MD, PhD

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

Takashi Kagari, PhD

Research Summary

Dr. Kagari's research has been focused on ADC pharmacology studies for the treatment of intractable cancer. He is interested in developing novel biologics as innovative anti-cancer drugs with new modalities.

Professional Experience/Awards

Dr. Kagari joined former Sankyo (current Daiichi Sankyo Co., Ltd.) in 1998 and started his carrier as an immunologist. He was a visiting scientist at UCSF Department of Medicine for two years beginning in 2007 before returning to the company. He was a Scientist in Biologics and Immuno-Oncology Labs and then senior director of Oncology Research Labs for ADC research in Daiichi Sankyo. He is currently Vice President of Discovery Research Laboratories I at Daiichi Sankyo Co., Ltd.

Education

MS Osaka University, Japan

PhD (Immunology) Osaka University, Japan

Abstract of the lecture

Antibody-drug conjugate (ADC) has attracted attention as a drug with a wider therapeutic window than existing chemotherapy because of its ability to efficiently deliver drugs to target areas in vivo. Daiichi Sankyo initiated ADC research to establish our own ADC technology using novel linker-payload system and developed proprietary DXd ADC technology. The major advantages of the DXd ADC technology are high and homogeneous drug-to-antibody ratio, original DNA topoisomerase I inhibitor payload showing potent antitumor activity with bystander antitumor effect, less potential safety concerns owing to the stable drug-linker limiting the release of free payload in the circulation, and short systemic half-life of the payload. A novel anti-HER2 ADC named trastuzumab deruxtecan (T-DXd; also known as DS-8201) was generated using this ADC technology. T-DXd was effective in patients with trastuzumab emtansine-treated HER2-positive breast cancer (BC), HER2-low BC, and other HER2-expressing solid tumors in published clinical trials. We are building a DXd ADC pipeline by applying this technology to a variety of targets to cover multiple cancer types, so that more patients can receive the benefits of drug therapy. This presentation will focus on the characteristics of our ADC technology and non-clinical pharmacology data on several DXd ADC programs.

Title: Biomarkers Predicting Response to Antibody Drug Conjugates: Should We Focus on the Target Antigens?

Speaker

Giuseppe Curigliano, MD, PhD

Professor at University of Milan and Head of Phase Division at IEO, ESMO Council Member, Italy

Chair/Moderator

Masakazu Toi, MD, PhD

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

Giuseppe Curigliano, MD, PhD

Research Summary

Dr. Curigliano's research experiences include principle or coinvestigator work in several phase I-II clinical trials with targeted agents, cytotoxic and endocrine agents in breast cancer. He has been also involved as principal investigator in several phase I studies with peptide vaccines for breast cancer (either in the adjuvant either in the metastatic setting). Dr Curigliano's research interests include the biology of breast cancer, predictive markers of response to therapy and new anti-cancer agents. He is the coordinator of a research platform on new drug development in breast cancer at European Institute of Oncology.

Professional Experience/Awards

Dr. Curigliano is a Professor of Medical Oncology at the University of Milano and the Head of the Division of Early Drug Development at the European Institute of Oncology, Italy. He is a member of the Italian National Health Council since 2018 and, in 2019, he served as Chair of the Scientific Committee of The Lega Nazionale Lotta ai Tumori. He served on the Scientific Committee for the St Gallen Conference since 2011, and was the Scientific Co-Chair in St Gallen 2017, 2019 and 2021. He served as the Scientific

Chair of the IMPAKT ESMO meeting that was held in Brussels in 2014 and as the Breast Cancer Track Chair of the ESMO 2014 meeting.

He served as Scientific Co-Chair of the ESMO Breast Cancer Congress in 2019, 2020 and 2021. He is an Editorial Board Member for Annals of Oncology, and serves as Co-Editor in Chief of The Breast, Co-Editor in Chief of Cancer Treatment Reviews, Associate Editor of the European Journal of Cancer, Editor of the Journal of Clinical Oncology.

Dr. Curigliano serves ESMO as Chair of the Guidelines Committee. He is the Chair of the ESMO Nomination Committee. He is member of the ESMO global Policy Committee and has been involved in the ESMO-WHO Cancer Workforce Project from 2019. He was awarded with the first ESO Umberto Veronesi Award in Vienna in 2017 and with the Fellowship of the European Academy of Cancer Sciences in Paris in 2017.He has contributed to over 440 peer-reviewed publications.

Education

MD Università Cattolica del Sacro Cuore, Policlinico Gemelli, Roma, Italy
PhD Università di Pisa, Italy

Abstract of the lecture

Antibody drug conjugates (ADCs) represent a cornerstone in the treatment of many cancers nowadays. The mechanism of action of ADCs is complex as they fulfil their function by binding a target on tumor cell membrane to deliver a cytotoxic payload; ADCs can also release the chemotherapeutic agent in the tumor microenvironment, exerting a “bystander” cytotoxic effect. The presence of a specific target antigen expressed on cancer cells has been for long considered crucial for ADCs and commonly required for the inclusion of patients in clinical trials with ADCs. To date, only ado-trastuzumab-emtansine (T-DM1), fam-trastuzumab deruxtecan-nxki (T-DXd) and mirvetuximab soravtansine-gynx (MIRV) are approved according to the expression of a target antigen in solid tumors. Given the ever-growing number of approved ADCs and considering those under investigation, it is essential to better define the target antigens’ role in predicting response to ADCs and find new biomarkers to guide their use. This is critical in those settings for which different ADCs are approved to select the best therapeutic sequence based on robust biomarkers. New methods for the assessment and quantification of targets’ expression, like molecular imaging and in-vitro assays, might be key tools to improve biomarker analysis and eventually deliver better outcomes by refined patient selection.

Reference

Unlocking the potential of antibody–drug conjugates for cancer therapy. Drago J. Z., Modi S. and Chandarlapaty S. *Nat Rev Clin Oncol* 2021; 18: 327–344.

Session 3

Molecular Targeting Therapy: Challenges in Control of the MAPK/ERK Pathway

3-1. Mechanisms Driving Evolution of TKI-Resistance in Non-Small Cell Lung Cancer

Speaker: : Aaron Hata, MD, PhD
(Assistant Professor, Medicine, Harvard Medical School, USA)

3-2. Splicing Vulnerability in RAS Q61 Mutant Cancers

Speaker: Yoshihisa Kobayashi, MD, PhD
(Staff Scientist, Div. Molecular Pathology, National Cancer Center Research Institute, Japan)

Title: Mechanisms Driving Evolution of TKI-Resistance in Non-Small Cell Lung Cancer

Speaker

Aaron Hata, MD, PhD

Assistant Professor, Medicine, Harvard Medical School, USA

Chair/Moderator

Hiroyuki Mano, MD, PhD

Director, National Cancer Center Research Institute, Japan

Aaron Hata, MD, PhD

Research Summary

The research goal of Dr. Hata's laboratory is to advance targeted therapies to benefit patients with lung cancer. Their research focuses on understanding the biological underpinnings of sensitivity and resistance to oncogene-directed targeted therapies and has identified mechanisms of clinical acquired resistance in *EGFR*-mutant, *KRAS*-mutant and *ALK*, *ROS1* and *RET* fusion-positive lung cancers. Most recently, they have begun to focus on understanding how cancer cells adapt and evolve during the course of therapy in order to identify vulnerabilities of drug tolerant cancer cells that might be exploited to prevent resistance from developing. Their studies are highly translational, integrating functional studies of patient-derived cell culture and mouse PDX models with analysis of clinical specimens, performed in close collaboration with clinicians in the MGH Thoracic Oncology group.

Professional Experience/Awards

Dr. Hata received his MD and Ph.D. degrees at Vanderbilt University in Nashville TN, where he studied the structure and function of prostaglandin receptors in the laboratory of Dr. Richard Breyer in the Department of Pharmacology. He completed an Internal Medicine residency at Brigham and Women's Hospital in Boston, followed by a Medical

Oncology fellowship at Dana Farber Cancer Institute and Massachusetts General Hospital. He performed his post-doctoral research in the laboratory of Dr. Jeffrey Engelman in the MGH Cancer Center, where he focused on understanding mechanisms of drug sensitivity and resistance to targeted therapies for lung cancer. In 2016, he joined the MGH Cancer Center faculty as Principal Investigator. Dr. Hata is currently an Assistant Physician at MGH and an Assistant Professor of Medicine at Harvard Medical School. He is also an Associate Member of the Broad Institute of Harvard and MIT, an Investigator in the Ludwig Center of Harvard and a Faculty Member of the Biological and Biomedical Sciences PhD Program at Harvard Medical School. He has been an Investigator on multiple multi-institutional collaborative teams including the Stand Up to Cancer Lung Cancer Dream Team, Stand Up to Cancer Tumor Evolution Convergence Team, Mark Foundation for Cancer Research – The Extol Project and the DFHCC Lung Cancer Spore. In 2023, he was elected to the American Society for Clinical Investigation.

Education

MD	2007	Vanderbilt University School of Medicine, USA
PhD	2005	Vanderbilt University School of Medicine, USA

Abstract of the lecture

Molecular targeted therapies have transformed the care of patients with oncogene-driven non-small cell lung cancers, however acquired drug resistance remains an unsolved clinical problem. Although many drivers of acquired drug resistance have been identified, the underlying molecular mechanisms that influence tumor evolution during treatment are incompletely understood. We recently demonstrated that mechanisms of clinical acquired drug resistance can evolve within drug tolerant cells that persist during therapy, suggesting that suppressing mechanisms of tumor evolution may prevent or delay the development of resistance. We find that lung cancer targeted therapies commonly used in the clinic can induce cytidine deaminase APOBEC3A (A3A), leading to sustained mutagenesis in drug-tolerant cancer cells persisting during therapy. Therapy-induced A3A promotes the formation of double-strand DNA breaks, increases genomic instability and leads to acquired mutations and structural variations. Moreover, deletion of A3A delays the emergence of drug resistant clones. These results implicate A3A as a driver of tumor evolution leading to acquired drug resistance and suggest that suppressing A3A may represent a potential therapeutic strategy to prevent or delay acquired resistance to lung cancer targeted therapy.

References

Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. Hata A. N., Niederst M. J., Engelman, J. A., et al. *Nature Medicine* 2016; 22: 262-9

Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. Yoda S., Lin J. J., Hata A. N., Shaw A. T., et al. *Cancer Discovery*. 2018; 8: 714-729.

Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. Piotrowska Z., Isozaki H., Hata A. N., Sequist L. V., et al. *Cancer Discovery* 2018; 8:1529-1539

Targeting FGFR overcomes EMT-mediated resistance in EGFR mutant non-small cell lung cancer. Raoof S., Mulford I. J., Hata A. N., et al. *Oncogene* 2019; 38: 6399-6413

Dagogo-Jack I., Yoda S., Hata A. N., et al. MET Alterations Are a Recurring and Actionable Resistance Mechanism in ALK-Positive Lung Cancer. *Clin Cancer Res* 2020; 26: 2535-2545

Lin J. J., Choudhury N. J., Hata A. N., Gainor J. F., et al. Spectrum of Mechanisms of Resistance to Crizotinib and Lorlatinib in ROS1 Fusion-Positive Lung Cancer. *Clin Cancer Res* 2021; 27: 2899-2909.

Noritaka T., Lin J. J., Hata A. N., Corcoran R. B., et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discov.* 2021; 11: 1913-1922

Shiba-Ishii A., Johnson T. W., Hata A. N., et al. Analysis of lorlatinib analogs reveals a roadmap for targeting diverse compound resistance mutations in ALK-positive lung cancer. *Nature Cancer* 2022; 3: 710-722

Title: Splicing Vulnerability in RAS Q61 Mutant Cancers

Speaker

Yoshihisa Kobayashi, MD, PhD

Staff Scientist, Division of Molecular Pathology, National Cancer Center Research Institute, Japan

Chair/Moderator

Hiroyuki Mano, MD, PhD

Director, National Cancer Center Research Institute, Japan

Yoshihisa Kobayashi, MD, PhD

Research Summary

Dr. Kobayashi has studied a wide variety of resistance mechanisms to tyrosine kinase inhibitors in EGFR or EML4-ALK lung cancer. These mechanisms include secondary mutations, bypass signaling from other oncogenic alterations, and histological transformation such as epithelial-mesenchymal transition. By using CRISPR-Cas9 technology for resistance studies, he developed unique models and discovered the critical weakness associated with splicing in RAS family genes, which are most frequently mutated in cancer. To develop innovative therapies for the cure of cancer, he has investigated mechanisms of carcinogenesis from the perspective of understanding how resistance develops.

Professional Experience/Awards

Dr. Kobayashi graduated with his MD from Mie University in 2008 and completed residency at Iizuka Hospital. He worked as a thoracic surgeon at Aichi Cancer Center (2010-2014) and Kindai University (2014-2018). He completed his PhD in 2017 with projects on EGFR-mutant lung cancer. He joined Pasi Janne lab at Dana-Farber Cancer Institute as a research fellow in 2018 and investigated projects on drug resistance in EGFR mutant lung cancer and novel RAS-targeted therapy. He moved to Division of Molecular Pathology at National Cancer Center Research Institute as a

scientist in 2021 and continues basic and translational research for the treatment of patients with cancer.

Dr. Kobayashi has received numerous awards, including such as The Young Scientists' Award, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology in 2023, Kiyoko and Paul Bourdarie-Goto Scientific Prize -Special Award in 2023, Shinoi-Kawai Award of the Japan Lung Cancer Society in 2022, and Young Scientist Award of the Japanese Cancer Association in 2021.

Education

MD 2008 Mie University, Japan
PhD 2017 Kindai University, Japan

Abstract of the lecture

Lung cancers inevitably develop resistance to targeted therapy, including EGFR tyrosine kinase inhibitors, despite the initial drastic response. One of the factors that contribute to the complexity of cancer biology is inter-tumor and intra-tumor heterogeneity. To simplify the models as much as possible, we utilized a single-cell clone derived from an EGFR mutant lung cancer cell line and employed CRISPR-Cas9 genome editing. These models demonstrated the potential for acquiring EGFR secondary mutations, fusion genes, or KRAS/BRAF mutations.

During our study on KRAS mutations as resistance mechanisms to EGFR inhibitors, we serendipitously discovered that the KRAS Q61K mutation cannot induce oncogenic effects without a concurrent silent mutation at G60. Generally, the role of silent mutations in cancer has not been systematically studied, leading to their disregard as mere noise in clinical mutational analyses. This co-occurrence of mutations was unique to KRAS Q61K among the KRAS/NRAS/HRAS variants, as confirmed by multiple genomic databases. Mechanistic analyses revealed that KRAS Q61K forms a cryptic splice site, resulting in alternative splicing and a non-functional KRAS Q61K protein. However, the concurrent silent mutation eliminates this cryptic splice site.

We also discovered another splicing vulnerability related to exonic splicing enhancers in the vicinity of the Q61 regions of KRAS, NRAS, and HRAS. By targeting these regions with antisense oligonucleotides, we induced aberrant exon skipping and inhibited growth in a mutant-selective manner. This strategy could serve as a novel approach for targeting RAS Q61 mutant cancers. Further discussion on future directions will be provided.

Reference

Kobayashi Y.*, et al. Silent mutations reveal therapeutic vulnerability in RAS Q61 cancers. *Nature* 2022;603(7900):335-342. *co-corresponding

Kobayashi Y., et al. Genomic and biological study of fusion genes as resistance mechanisms to EGFR inhibitors. *Nat Commun* 2022;13(1):5614.

Cooper A. J.*, Kobayashi Y.*, et al. Identification of a Ras-Activating Tmem87a-Rasgrf1 Fusion in an Exceptional Responder to Sunitinib with Non-Small Cell Lung Cancer. *Clin Cancer Res* 2020;26(15):4072-4079. *co-first

Kobayashi Y., et al. EGFR T790M and C797S Mutations as Mechanisms of Acquired Resistance to Dacomitinib. *J Thorac Oncol* 2018;13(5):727-731.

Kobayashi Y., et al. Characterization of EGFR T790M, L792F, and C797S mutations as mechanisms of acquired resistance to afatinib in lung cancer. *Mol Cancer Ther* 2017;16: 357-64.

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Session 4

Special Session

New Immunotherapy Approaches for Microsatellite Stable (MSS) Colorectal Cancer

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

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Title: New Immunotherapy Approaches for Microsatellite Stable (MSS) Colorectal Cancer

Speaker

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

Chair/Moderator

Yuko Kitagawa, MD, PhD

Professor, Department of Surgery, Graduate School of Medicine, Keio University, Japan

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 Universitat Autònoma de Barcelona, Spain
PhD 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 dismal, 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 with the main purpose of boosting immunogenicity. In this presentation, we will discuss these new therapeutic approaches in selected biomarker-defined populations.

Session 5

Deepening the Understanding of Cancer and Immunity

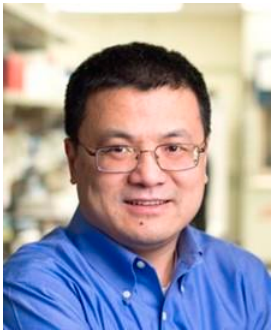
5-1. Integrating Systems Immunology with Metabolism and Cancer

Speaker: Hongbo Chi, PhD
(Professor, St. Jude Children's Research Hospital, USA)

5-2. Gamma Delta T Cells Offer a Conserved Mechanism that Discriminates Cancer Cell Pathology from Healthy Cell Physiology

Speaker: Adrian Hayday, PhD (Professor, King' s College London, UK)

Title: Integrating Systems Immunology with Metabolism and Cancer



Speaker

Hongbo Chi, PhD

Professor, Robert G. Webster Endowed Chair in Immunology, Department of Immunology, St. Jude Children's Research Hospital, USA

Chair/Moderator

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 Research, Japan

Hongbo Chi, PhD

Research summary

Dr. Chi's laboratory has a long-standing interest in immune signaling and cell metabolism underlying the differentiation and function of T cells, a central cell type in adaptive immunity and cancer immunotherapy. They use a combination of experimental systems including mouse genetics, cellular immunology and biochemistry, as well as models of cancer, infection an autoimmune disease. Recently, they apply systems biology approaches, such as proteomics, metabolomics, single cell RNA-sequencing (scRNA-seq), CRISPR screening and integrative network analysis, to reconstruct metabolic signaling circuits and identify new therapeutic targets. His laboratory has made important discoveries in understanding the principle of metabolic reprogramming for immune cell fate, state and tolerance.

Professional experience

Dr. Hongbo Chi received his PhD from the University of Rochester, and his postdoctoral training with Dr. Richard Flavell from Yale University School of Medicine. In 2007, he started his independent research program at St. Jude Children's Research Hospital, where he is currently a Member (Professor) in the Department of Immunology, and Robert G. Webster Endowed Chair in Immunology.

His research focuses on mechanisms of immune signaling and metabolism, in particular how mTOR and other signaling pathways interplay with metabolic programs in T cell fate decisions and dendritic cell biology. Among the highlights of the work, his laboratory has discovered the critical importance of mTOR signaling, metabolism and autophagy in the differentiation and function of effector and regulatory T cells, the control of T cell quiescence and antigen-triggered exit from quiescence, and the regulation of autoimmune, infectious and malignant diseases.

His work is highly regarded and widely referenced, earning him a place on the 2020–2022 Highly Cited Researchers lists. He has recently received an NIAID R37 merit award and an NCI outstanding investigator award.

Education

BA	1994	Shandong University, China
PhD	2001	University of Rochester, USA

Abstract of the lecture

The goals of our research program are to discover the mechanisms linking the metabolic state of immune cells (immunometabolism) with tissue homeostasis and function, and to use these insights for better treatments for cancer and other diseases. We are particularly interested in understanding metabolic drivers, nutrient signaling pathways and systems-level regulatory networks in basic T cell and dendritic cell biology and antitumor immunity. To gain an integrative view, we combine the traditional hypothesis-driven or 'reductionist' approach with systems biology principles, including in vivo CRISPR screening, systems proteomics and data-driven network algorithms, to identify new concepts and therapeutic targets for immunometabolism that cannot be surmised from simpler systems. I will discuss our recent progresses in target discovery in T cells and nutrient-mediated intercellular signaling in the tumor microenvironment.

References

Targeting REGNASE-1 programs long-lived effector T cells for cancer therapy. Wei J., Long L., Chi H., et al. *Nature* 2019; 576: 471-476. (highlighted by News and Views "Antitumour T cells stand the test of time" in the same issue of *Nature*, and *Nat Rev Drug Discov*)

CRISPR screens unveil signal hubs for nutrient licensing of T cell immunity. Long L., Wei J., Chi H., et al. *Nature* 2021; 600: 308-313.

Lipid signalling enforces functional specialization of T_{reg} cells in tumours. Lim S. A., Wei J., Chi H., et al. *Nature* 2021; 591: 306-311. (highlighted by News and Views "Cancer aided by greasy traitors" in the same issue of *Nature*)

In vivo CRISPR screening reveals nutrient signaling processes underpinning $CD8^+$ T cell fate decisions. Huang H., Zhou P., Chi H., et al. *Cell* 2021; 184: 1245-1261 (highlighted by Preview "How to make a better T cell: in vivo CRISPR screens have some answers" in the same issue of *Cell*).

Metabolic control of TFH cells and humoral immunity by phosphatidylethanolamine. Fu G., Guy C. S., Chi H., et al. *Nature* 2021; 595: 724–729.

cBAF complex components and MYC cooperate early in CD8+ T cell fate. Guo A., Huang H., Chi H.*, Green D. R.*, et al. (* shared senior authorship). *Nature* 2022; 607: 135-141.

Title: Gamma Delta T Cells Offer a Conserved Mechanism that Discriminates Cancer Cell Pathology from Healthy Cell Physiology

Speaker

Adrian Hayday, PhD

Professor of Immunobiology at King's College London,
Principal Group Leader, The Francis Crick Institute, UK

Chair/Moderator

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 Research, Japan

Adrian Hayday, PhD

Research summary

Dr. Hayday studies how T cells can react very rapidly to many forms of dysregulation in the body's tissues. To explain this, his laboratory has developed a theory called 'lymphoid stress surveillance', that focuses on sets of molecules expressed by dysregulated cells that are recognized by T cells present at body surfaces such as the skin, gut, and lung. This surveillance system exists in parallel with the recognition of danger by myelomonocytic cells but is distinct from it. Thus, 'Lymphoid stress surveillance' can explain how T cells bearing γδ T cell receptors can recognize cells that could eventually turn into tumors. This cancer surveillance mechanism is also distinct from neoantigen recognition by alpha beta T cells and it thereby offers a capacity for the recognition of cancer cells that have low frequencies of mutation and therefore have few neoantigens. Recently, Dr Hayday and his coworkers demonstrated that the poorly understood butyrophilin-like (BTNL) gene family plays a central role in the recognition of healthy epithelial cells by γδ T cells. By being able to recognize BTNL molecules on healthy epithelial cells and "stress antigens" on cancerous cells, γδ T cells have a natural therapeutic window that prevents their inappropriate attack on normal tissues.

Applying these ideas, Dr Hayday's team is exploring the potential for new cancer therapies based on γδ T cells, and clinical trials commenced in 2021. The part of his team working on this is based at Guy's Hospital, London, which is affiliated to the faculty of life sciences and medicine at King's College.

Professional experience

Dr. Hayday began studying immunology as a postdoctoral researcher in 1982 at Massachusetts Institute of Technology (MIT) supervised by Susumu Tonegawa, where he identified the molecular basis of oncogene activation in Burkitt's lymphoma. Thereafter, he first described the genes defining γδ T cells, an evolutionarily conserved yet wholly unanticipated set of lymphocytes. At Yale University, King's College London, and the Francis Crick Institute, Dr. Hayday established that γδ T cells are distinct from other T cells, commonly monitoring body-surface integrity rather than specific infections. Their rapid responses to tissue dysregulation offer protection from carcinogenesis, underpinning Dr. Hayday's and others' ongoing initiatives to employ γδ T cells for immunotherapy.

Dr. Hayday has received numerous awards, including the William Clyde DeVane Medal, Yale's highest honor for scholarship and teaching. He is an honorary member of the British Society for Immunology and is an elected Fellow of the Royal Society and of the Academy of Medical Sciences.

Education

BA	1978	Queens' College, Cambridge, UK
PhD	2001	Imperial College London, UK

Abstract of the lecture

Current approaches to cancer immunotherapy borrow directly from antigen-specific, adaptive CD8 T cell responses to virus infection. In cancers such as those induced by papilloma viruses or Epstein Barr virus, the antigens are viral peptides presented by MHC, whereas in other cancers, "neo-antigens" are derived from autologous proteins mutated as a result of genome instability. Therapeutic "checkpoint inhibitors" promote such T cell responses and can be highly efficacious. However, they are also efficacious in tumours lacking MHC and/or with low mutational burden that are therefore not suited to αβ T cell surveillance. These favourable clinical outcomes reflect an alternative means of tumour-targeting mediated by γδ T cells that recognise combinatorial markers of cell pathology rather than specific antigens. Central to this is the unique property of the γδ T cell receptor (TCR) which can actively distinguish cancerous cells, that γδ T cells can attack, from healthy cells to which γδ T cells provide homeostatic support. This translates to a natural and practical therapeutic window that can explain promising clinical results from the direct application of γδ T cells as cancer therapeutics, either unmodified or coupled to CAR-T. The presentation will focus on the underlying immunological mechanisms and their practical application.

References

Gammadelta T cells and the lymphoid stress-surveillance response. Hayday A. C., *Immunity* 2009; 31(2):184-96.

Epithelia Use Butyrophilin-like Molecules to Shape Organ-Specific γδ T Cell Compartments. Di Marco Barros R., Roberts N. A., Hayday A. C., et al. *Cell* 2016; 167: 203-218.

A local human Vδ1 T cell population is associated with survival in nonsmall-cell lung cancer. Wu Y., Biswas D., Hayday A. C., Swanton C., et al. *Nat Cancer* 2022; 3: 696-709.

Session 6

Cancer Genomics & Biology: Basics & Applications

6-1. Evolutionary Histories of Breast Cancer and Related Clones

Speaker: Seishi Ogawa, MD, PhD (Professor, Kyoto University, Japan)

6-2. WNK1 Signaling Regulates Amino Acid Transport and mTORC1 Activity to Sustain AML Growth

Speaker: Kristian Helin, PhD
(Professor, The Institute of Cancer Research, London, UK)

Title: Evolutionary Histories of Breast Cancer and Related Clones

Speaker

Seishi Ogawa, MD, PhD

Professor, Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Japan

Chair/Moderator

Chikashi Ishioka, MD, PhD

Professor, Institute of Development, Aging and Cancer, Tohoku University, Japan

Seishi Ogawa, MD, PhD

Research summary

It is true that “genetic defects cause cancers.” However, it is more complicated and difficult to fully understand cancers than implied by such a simple statement. Cancer is consisted of the genetically heterogeneous multiple cells which are derived from cancer stem cells acquiring somatic mutations during the sequential divisions. Recently, the advanced sequencing technologies help us to identify a huge amount of new genetic abnormalities. However, it is still remain to be elucidated how the functional relevance of these genetic events, especially, the clonal selections of cancer cells escaping form the immunogenic reactions establishes the malignant characteristics with genetic heterogeneity.

Professional Experience/Awards

Dr. Ogawa is a Professor at Kyoto University –Kyoto, since 2013 and is also invited as a visiting professor at Karolinska Institute, Sweden. He has been the head of the department of Pathology and Tumor Biology since 2013 developing work on genome analysis of human cancers. His scientific contribution has been central to understand the pathogenesis of myelodysplastic syndromes, clear cell renal carcinoma,

neuroblastoma and other hematological cancers through identification of key genetic alterations and mutations. The recent topics of his recent studies are clonal origin of cancer, including clonal hematopoiesis, which he is intensively studying using a large cohort of patients and micro-scale sampling and high-throughput sequencing and single-cell sequencing. He has received prestigious awards, most recently, Uehara Prize (2017), Culture, Sports, Science and Technology Minister's Commendation (2017), Princes Takamatsu Cancer Research Fund Prize (2017), Takamine Prize (2018), Medal with Purple Ribbon (2018), Erwin von Bealz Prize (2019), Minister of Education Award, Award for Academic Startups (2022).

Education

MD	1988	University of Tokyo, Japan
PhD	1993	University of Tokyo, Japan

Abstract of the lecture

Recent studies have documented frequent evolution of clones carrying common cancer mutations in apparently normal tissues, which are implicated in cancer development. However, our knowledge is still missing regarding what additional driver events take place in what order, before one or more of these clones in normal tissues ultimately evolve to cancer. Here, using phylogenetic analyses of multiple micro-dissected samples from both cancer and non-cancer lesions, we show unique evolutionary histories of breast cancers harbouring der(1;16), a common driver alteration found in approximately 20% of breast cancers. The approximate timing of early evolutionary events was estimated from the mutation rate measured in normal epithelial cells. In der(1;16)(+) cancers, the derivative chromosome was acquired from early puberty to late adolescence, followed by the emergence of a common ancestor by the patient’s early 30s, from which both cancer and non-cancer clones evolved. Replacing the pre-existing mammary epithelium in the following years, these clones occupied a large area within the premenopausal breast tissues by the time of cancer diagnosis. Unexpectedly, evolution of multiple independent cancer founders from the non-cancer ancestors was common, contributing to intratumour heterogeneity. Our findings provide new insight into the evolution of breast cancer.

Title: WNK1 Signaling Regulates Amino Acid Transport and mTORC1 Activity to Sustain AML Growth

Speaker

Kristian Helin, PhD

Professor, Epigenetics and Cancer
Chief Executive and President
The Institute of Cancer Research, London, UK

Chair/Moderator

Chikashi Ishioka, MD, PhD

Professor, Institute of Development, Aging and Cancer,
Tohoku University, Japan

Kristian Helin, PhD

Research summary

Dr. Helin's team studies the role of chromatin-associated proteins (epigenetics) in the regulation of transcription, cell fate decisions and in cancer. The team is also using functional genetic screens to identify potential novel targets for the development of anti-cancer therapy.

Professional Experience/Awards

Dr. Helin is the CEO and President of The Institute of Cancer Research (ICR) in London. Moreover, he is a professor in Epigenetics and Cancer at the ICR and the University of London. He obtained a MSc in Chemical Engineering from the Technical University of Denmark and a PhD from University of Copenhagen. He was a research fellow at Harvard Medical School, started his own research group at the Danish Cancer Society in 1994 and became subsequently a founding member of the Dept of Experimental Oncology at the European Institute of Oncology in Milan, Italy. From 2003 to 2018 he was the founding director of the Biotech Research and Innovation Centre at

University of Copenhagen and in 2018-2021 Prof Helin was the Chair of the Cell Biology Program and the Director of Center for Epigenetics Research at Memorial Sloan Kettering Cancer Center, New York.

The Helin laboratory has made several seminal discoveries in the field of cell cycle control, epigenetics and cancer. In addition to providing novel insights into mechanisms regulating transcription, stem cell identity and differentiation, the work in Prof Helin's lab has led to the establishment of the biotech companies EpiTherapeutics and Dania Therapeutics. Dr. Helin is elected as Foreign Member of the Royal Society (UK), Fellow of the Academy of Medical Sciences (UK), member of the European Molecular Biology Organisation (EMBO) and the Royal Danish Academy of Science and Letters. He has received several prestigious awards for outstanding biomedical research, including the Novo Nordisk Prize, the Carlsberg Prize and the Anders Jahre's Prize, and serves in several editorial boards, committees of advisory boards and grant committees.

Education

MS 1988 Technical University of Denmark, Denmark
PhD 1991 University of Copenhagen, Denmark

Abstract of the lecture

Despite recent advances in understanding the underlying molecular genetics and cytogenetic alterations of AML, and the successful development of new targeted therapies for patients with specific genetic lesions, primary resistance and relapse remain a challenging issue.
To identify protein kinases that are essential for AML cells, we employed a CRISPR/Cas9–based negative selection screen. The screen led to the identification of 37 kinases, including CDK1, CDK9, ATR and JAK2, known to be important for AML maintenance. Recently, we validated RIOK2, one of the top dropout hits from the screen, as an essential dependency in AML. Moreover, we identified WNK1 (With-No-lysine(K) kinase 1), as another top dropout kinase hit in the screen.
WNK1 belongs to a subfamily of four atypical serine-threonine kinases characterised by their lack of a conserved catalytic lysine in the kinase subdomain II that is crucial for ATP binding. WNK1 plays a critical role in ion transport through its effector kinases OXSR1 and STK39/SPAK. WNK1-mediated phosphorylation and activation of the OXSR1/STK39 kinases, controls the activity of the SLC12 family of cation-coupled chloride co-transporters.
At the meeting, I will present data showing that genetic depletion and pharmacological inhibition of WNK1 or its downstream phosphorylation targets OXSR1 and STK39 strongly reduce cell proliferation and induce apoptosis in leukaemia cells *in vitro* and *in vivo*. Furthermore, I will show that the WNK1-OXSR1/STK39 pathway controls mTORC1 signalling via regulating amino acid uptake through a mechanism involving the phosphorylation of amino acid transporters, such as SLC38A2.
Taken together our results demonstrate a critical role of the WNK1-OXSR1/STK39 pathway in regulating amino acid uptake and in AML progression. Moreover, our mode of action studies suggests that WNK1 and OXSR1/STK39 inhibitors could be effective in a broad range of cancer types.

Session 7

Breakthrough Technology 1: Single Cell Analysis

Dissecting Human Gliomas by Single-Cell Genomics

Speaker: Mario L. Suvà, MD, PhD
(Associate Professor, Pathology, Harvard Medical School, USA)

Title: Dissecting Human Gliomas by Single-Cell Genomics

Speaker

Mario L. Suvà, MD, PhD

Associate Professor, Pathology, Massachusetts General Hospital and Harvard Medical School, USA
Institute Member at the Broad Institute of MIT and Harvard
Co-Leader, DF/HCC Neuro-Oncology Program
Co-Director, Cancer Program, Harvard Stem Cell Institute

Chair/Moderator

Hitoshi Nakagama, MD, PhD

President, National Cancer Center, Japan

Mario L. Suvà, MD, PhD

Research summary

Dr. Suvà's laboratory focuses on the biology of brain tumors, both in adults and children. A particular effort of the laboratory is on dissecting the heterogeneity of diffuse gliomas and relating transcriptional and genetic programs of individual cancer cells. Dr. Suvà directed landmark studies characterizing glioblastoma, oligodendroglioma, astrocytoma, pediatric gliomas and medulloblastoma with single-cell genomic technologies, shedding light on tumor heterogeneity, tumor classification, glioma cell lineages, cancer stem cell programs, tumor evolution and the composition of the tumor microenvironment.

Professional Experience/Awards

Dr. Suvà is a physician-scientist in the Department of Pathology at Massachusetts General Hospital (MGH) and at the Broad Institute of MIT and Harvard. Suvà's expertise is in neuro-oncology, single-cell genomics and chromatin analysis.

Dr. Suvà obtained his Ph.D. in Lausanne, Switzerland, studying cancer stem cells in gliomas and sarcomas. He earned his M.D. from the University of Lausanne and his certification in Neuropathology from the Swiss Medical Association. He did his post-doctoral research at MGH and the Broad Institute, applying chromatin analysis and functional approaches to identify master regulators of glioma stem cell programs.

Dr. Suvà has received 15 awards for his seminal contributions, including most recently, the MERIT Award from the National Cancer Institute (2020), Emerging Leader Award from the Mark Foundation (2020), and Neuro-Oncology Scientific Award, American Academy of Neurology (2017). Dr. Suvà has a strong interest in teaching and mentoring students, residents and post-doctoral fellows beginning as a medical school student to his current faculty position at MGH and Harvard.

Education

MD	1999	University of Lausanne, Switzerland
PhD	2009	University of Lausanne, Switzerland

Abstract of the lecture

My laboratory at Massachusetts General Hospital and the Broad Institute studies pediatric and adult brain tumors with single-cell genomic technologies. We leverage a systems biology approach to characterize and target the cellular states that drive gliomas. In an effort to comprehensively characterize the ecosystems of pediatric and adult gliomas, we have brought single-cell genomics to the clinic in a spectrum of clinical entities. Our efforts have offered new insights into cancer stem cell programs, cancer cells lineages of differentiation, and the interplay between neural development and genetics in IDH-mutant oligodendroglioma (Tirosh et al., Nature 2016), IDH-mutant astrocytoma (Venteicher et al., Science 2017), pediatric gliomas with histone H3 mutation (Filbin et al., Science 2018), medulloblastoma (Hovestadt et al, Nature, 2019) and IDH-wildtype glioblastoma (Neftel et al, Cell 2019; Chaligne et al, Nature Genetics 2021). Our studies are also characterizing and refining our understanding of the composition of the tumor micro-environment in gliomas, with important therapeutic implications (Mathewson et al, Cell, 202; Hara et al, Cancer Cell 2021). Overall, our works have dissected with great details the circuitries of cancer and immune cells in human brain tumors, offering novel insights into their biology and into vulnerabilities that could be leveraged for their management. I will discuss these and new ongoing studies during my presentation at the IAAO 2023 Symposium.

Session 8

Breakthrough Technology 2: Application of CAR-T

8-1. CAR-T Cell Therapies in Solid Tumors – BNT211 Targeting CLDN6 in Combination with an RNA Vaccine and Beyond

Speaker: Benjamin Rengstl, MD, PhD
(Director, Immunoreceptor Therapy, BioNTech SE, Germany)

8-2. Drivers in CAR-T Cell Therapy

Speaker: Marcela V. Maus, MD, PhD
(Assistant Professor, Medicine, Harvard Medical School, USA)

Title: CAR-T Cell Therapies in Solid Tumors – BNT211 Targeting CLDN6 in Combination with an RNA Vaccine and Beyond

Speaker

Benjamin Rengstl, MD, PhD

Director Clinical Development & Director Immunoreceptor Therapy, BioNTech SE

Chair/Moderator

Kiyohiko Hatake, MD, PhD

Professor, Akasaka Sanno Medical Center, Japan

Benjamin Rengstl, MD, PhD

Research summary

To improve CAR-T cell therapy, Dr. Rengstl's team pioneered an in vivo expansion concept based on a liposomally formulated RNA vaccine for systemic delivery of CAR antigen (CAR-T cell Amplifying RNA Vaccine, CARVac). A FIH clinical trial assessing BioNTech´s novel CLDN6-specific CAR in combination with CARVac is currently ongoing. Furthermore, he is leading multiple programs to develop next generation cell- and RNA-based immunotherapies and further takes technology agnostic approaches to create new strategies for controlled modulation of the immune system.

Professional Experience/Awards

Dr. Rengstl is a trained physician and biochemist. Since 2009, he is exploring the potential of the immune system to combat cancer and infectious diseases. Between 2014 and 2016, he received his approbation as well as a PhD and a MD degree from the University of Frankfurt, Germany. During his postdoctoral training, he developed chimeric antigen receptor (CAR)-engineered T-cell therapies against lymphomas and

got trained in clinical pathology. In 2017, he joined BioNTech SE located in Mainz to develop a clinical CAR-T cell candidate for treatment of solid tumors.

Education

2014 PhD Biochemistry	University of Frankfurt, Germany
2016 Medical license	University of Frankfurt, Germany
2017 MD Tumorimmunology	University of Frankfurt, Germany

Abstract of the lecture

Chimeric antigen receptor (CAR)-T cell therapy has been successfully established to treat B-cell malignancies, however clinical efficacy in solid tumors is still rare due to the lack of safe targets and CAR-T cell persistence. Multiple new developments are emerging to clinic, but BioNTech is pioneering the first novel/novel combination to improve CAR-T cell therapy in solid tumors.
BNT211-01 (NCT04503278) is evaluating a CAR-T cell therapy targeting the oncofetal antigen claudin 6 (CLDN6) as either a monotherapy or in combination with an mRNA vaccine (CARVac) designed to stimulate CLDN6 CAR-T cells *in vivo*. The ongoing first-in-human trial assesses CLDN6 CAR-T cell therapy ± CARVac after lymphodepleting chemotherapy in patients with relapsed/refractory CLDN6-positive solid tumors. Key endpoints include safety, tolerability, and anti-tumor efficacy.
Twenty-two patients, 13 with testicular germ cell tumors (GCT), 4 with epithelial ovarian carcinoma, and 5 with other solid tumors received $1x10^7$ or $1x10^8$ CLDN6 CAR-T cells ± CARVac. Robust engraftment and expansion were observed, and both treatments were well tolerated. Dose-limiting toxicities occurred in 2 patients at the higher dose level, resolving without sequelae. Cytokine release syndrome was reported in 10 patients (grade 3 in 1 and ≤ grade 2 in 9 patients). Grade 1 neurotoxicity occurred in 1 patient. Most treatment-emergent adverse events ≥ Grade 3 were related to chemotherapy or were asymptomatic transaminase/lipase elevations. The overall response rate (ORR) was 33%, with one complete and 6 partial responses in 21 evaluable patients. Seven patients had stable disease (disease control rate (DCR) of 67%). The highest response rate was observed in GCT patients at the higher dose level (ORR 57%, DCR 85%), with 42% progression-free survival at 6 months.
In this multicenter study, CLDN6 CAR-T cells ± CARVac had a manageable safety profile and induced encouraging responses in heavily pretreated patients with CLDN6-positive tumors.

References

BNT211: A Phase I trial to evaluate safety and efficacy of CLDN6 CAR-T cells and CLDN6-encoding mRNA vaccine-mediated in vivo expansion in patients with CLDN6-positive advanced solid tumors. Mackensen A., Haanen J. B. A. G., Rengstl B., Sahin U., et al. ESMO 2022 (LBA38)

BNT211: A Phase I trial to evaluate safety and efficacy of CLDN6 CAR-T cells and CARVac-mediated in vivo expansion in patients with CLDN6-positive advanced solid tumors. Haanen J. B. A. G., Mackensen A., Rengstl B., Sahin U., et al. AACR 2022 (CT002)

An RNA vaccine drives expansion and efficacy of claudin-CAR-T cells against solid tumors. Reinhard K., Rengstl B., Sahin U., et al. *Science* 2020; 367: 446-453.

Title: Drivers in CAR-T Cell Therapy

Speaker

Marcela V. Maus, MD, PhD

Assistant Professor, Medicine, Harvard Medical School, USA
Director of Cellular Immunotherapy, Cancer Center, Massachusetts General Hospital, USA

Chair/Moderator

Kiyohiko Hatake, MD, PhD

Professor, Akasaka Sanno Medical Center, Japan

Marcela V. Maus, MD, PhD

Research summary

The goal of Dr. Maus's lab is to design and evaluate next generation genetically-modified (CAR) T cells as immunotherapy in patients with cancer. We will test the modified T cells in vitro, in small animal models, and if there is evidence that the treatment is promising, in patients who are eligible and wish to participate in clinical trials. The MGH Cellular Immunotherapy Program directed by Dr. Maus aims to translate new findings in the field of immunology and cell therapies from the laboratory to treat patients with cancer, and to learn from the clinic by analyzing immune biomarkers and understanding the mechanisms of how immunotherapy works, the toxicities it can cause, and the mechanisms of relapse if they occur . The Cellular Immunotherapy Program includes her laboratory and also core laboratories and translational units that facilitate bridging the lab and the clinic.

Professional Experience/Awards

Dr. Maus is currently an Associate Professor at Harvard Medical School, the Paula O'Keefe Chair in Oncology and Director of Cellular Immunotherapy at Massachusetts General Hospital (MGH) Cancer Center, an Attending Physician in the Hematopoietic Cell Transplant and Cell Therapy division of Oncology at MGH. She is an Associate Member of the Broad Institute of Harvard and MIT, and an Associate Member of the

Ragon Institute of MGH, MIT, and Harvard. Dr. Maus is internationally known for her work as a translational physician-scientist in the field of immunology, particularly as it relates to T-cell immunotherapies and cellular therapies in the treatment of cancer. Her laboratory focuses on the biology of human T cell activation, co-stimulation, and memory, and on the application of human T cell therapies to human disease, including forward and reverse translation of engineered T cell therapies in early-phase clinical trials. She has authored over 100 papers indexed in PubMed and holds three NIH R01 grants and several Investigational New Drug applications.

Dr. Maus holds an undergraduate degree from Massachusetts Institute of Technology (MIT) and graduate degrees (MD, PhD) from University of Pennsylvania. Dr. Maus trained in internal medicine at University of Pennsylvania and in hematology and medical oncology at Memorial Sloan Kettering Cancer Center, is board-certified in these three disciplines, and practices medical oncology. She also serves on several scientific and clinical advisory boards for the biotechnology industry as well as external academic medical centers

Education

MD	2005	University of Pennsylvania School of Medicine
PhD	2003	University of Pennsylvania School of Medicine

Abstract of the lecture

Dr. Maus will discuss recent findings relevant to CAR T cell therapies, focusing on the mechanisms underlying CAR T cell functions and how they impact clinical results. Topics will include the role of interferón gamma and cell death signaling in CAR-T cell/tumor interactions, and germline and transcriptional correlates of CAR T cell efficacies and toxicities. In addition, Dr. Maus will review recent insights into CAR design and mechanisms related to clinical effects.

References

Distinct cellular dynamics associated with response to CAR-T therapy for refractory B cell lymphoma. Haradhvala N. J., Leick M. B., Maus M. V., et al. *Nat Med* 2022; 28:1848-1859.

Understanding CAR T cell-tumor interactions: Paving the way for successful clinical outcomes. Korell F., Berger T. R., Maus M. V. *Med* 2022; 3: 538-564.

Non-cleavable hinge enhances avidity and expansion of CAR-T cells for acute myeloid leukemia. Leick M. B., Silva H., Maus M. V., et al. *Cancer Cell* 2022 May 9; 40: 494-508.

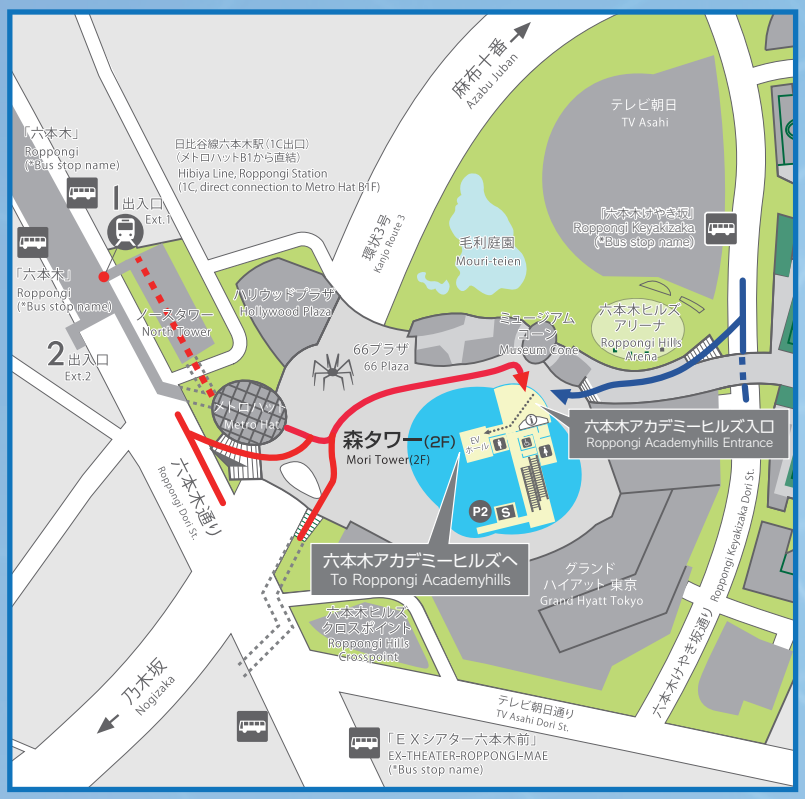
CAR T cell killing requires the IFNγR pathway in solid but not liquid tumours. Larson R. C., Kann M. C., Maus M. V., et al. *Nature* 2022; 604: 563-570.

Blockade or Deletion of IFNγ Reduces Macrophage Activation without Compromising CAR T-cell Function in Hematologic Malignancies. Bailey S. R., Vatsa S., Maus M. V., *Blood Cancer Discov* 2022; 3: 136-153.

Access Map

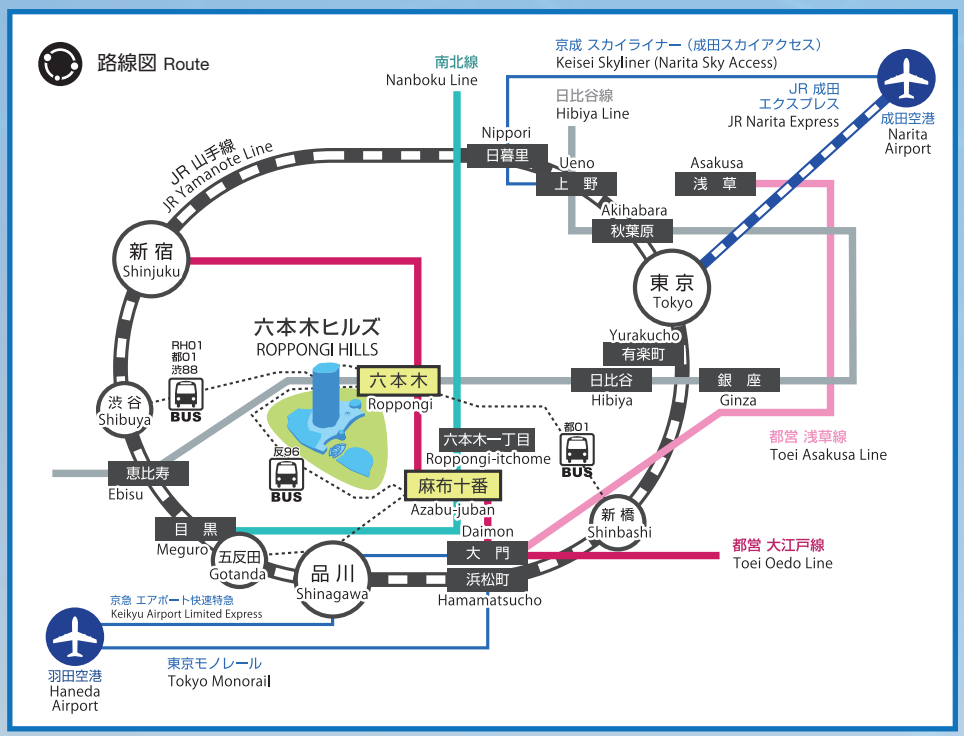
Place: Roppongi Academyhills

49F, Roppongi Hills Mori Tower, 6-10-1 Roppongi,
Minato-ku, Tokyo 106-6149



Subway:
Tokyo Metro Hibiya Line Roppongi Station / 3 min. walk from Exit 1C
(Direct link to concourse)

Toei Subway Oedo Line Roppongi Station / 6 min. walk from Exit 3



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