

会议议程 Agenda

开幕致辞 Opening Remarks

主持人：叶定伟 副院长 Compere: Dingwei Ye, Vice President of FUSCC

14:00-14:15	郭小毛 Xiaomao Guo	复旦大学附属肿瘤医院院长 President of FUSCC
	松本邦夫 Kunio Matsumoto	日本国立金沢大学癌症研究所副所长 Vice President of CRIKU
	校领导	复旦大学 Fudan University

第一部分 Session I

主席：叶定伟 教授 Chair: Prof. Dingwei Ye (FUSCC)

14:20-14:50	松本邦夫 教授 Prof. Kunio Matsumoto	肿瘤生物学及 HGF-Met 分子靶向药物的开发 Tumor Biology and Drug Discovery Targeting HGF-Met
14:50-15:20	胡欣 副教授 Prof. Xin Hu	BRCA1 相关 A 蛋白复合体的功能研究：DNA 损伤修复 & 乳腺导管形成缺陷 Multiple Roles of the BRCA1 A Complex: From DNA Damage Repair to Mammary Duct Morphogenesis
15:20-15:50	佐藤博 教授 Prof. Hiroshi Sato	膜型基质金属蛋白酶（MT1-MMP）在肿瘤侵袭和转移中的作用 Roles of Membrane-Type Matrix Metalloproteinase-1 in Tumor Invasion
15:50-16:00	茶歇 Tea Break	

第二部分 Session II

主席：松本邦夫 教授 Chair: Prof. Kunio Matsumoto (CRIKU)

16:00-16:30	胡维国 教授 Prof. Weiguo Hu	CD59 促进肿瘤细胞对抗体治疗产生耐药 CD59 Confers Resistance to Antibody-Based Therapy on Cancer Cells
16:30-17:00	矢野聖二 教授 Prof. Seiji Yano	肺癌的分子靶向治疗 Molecular Targeted Therapy for Lung Cancer
17:00-17:30	孙孟红 教授 Prof. Menghong Sun	肿瘤专科医院组织库运行的探讨 Management of Cancer Center Tissue Bank





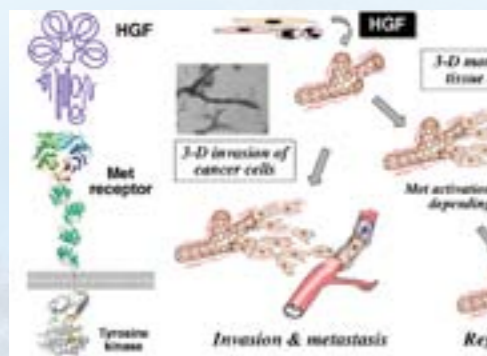
Prof. Kunio Matsumoto

Director, Division of Tumor Dynamics and Regulation
Kanazawa University Cancer Research Institute, Japan

Tumor Biology and Drug Discovery Targeting HGF-Met

Abstract:

Hepatocyte growth factor (HGF) was originally discovered as a mitogenic protein for mature hepatocytes (figure). HGF has four repeat of unique structural domain, Kringle domains. HGF exerts various biological activities, including cell proliferation, 3-D morphogenesis, migration, and anti-apoptosis in diverse biological processes. The receptor for HGF is Met tyrosine kinase. HGF plays critical roles in dynamic morphogenesis and regeneration of various tissues such as the liver. Met receptor in injured tissue is activated upon HGF-binding, whereas Met receptor in non-injured tissues is not susceptible to activation even after HGF-stimulation, suggesting an unique injury-related mechanism for selective Met activation in injured tissues. In cancer tissues, however, aberrant activation of the Met/HGF receptor is tightly associated with malignant progression of cancer, i.e., 3-D invasion, metastasis, angiogenesis, and drug resistance.



During the past few decades, the success of drug development targeting growth factors and their receptor tyrosine kinases in human cancer has triggered new therapeutic strategy for treating cancer. Based on its close involvement — not only in tumor development, invasion, and metastasis but also in resistance to anticancer therapies — the HGF Met pathway has become a hot target in anticancer drug development. Different types of HGF-Met inhibitors have been developed, including NK4 (a competitive inhibitor and a fragment of HGF), small molecule inhibitors for Met tyrosine kinase, and neutralizing monoclonal antibodies against HGF or Met. Preclinical and clinical development of HGF-Met inhibitors will provide further advance in molecular targeted therapy of cancer.

Reviews:

1. Matsumoto K, Nakamura T. *Hepatocyte growth factor and the Met system as a mediator of tumor-stromal interactions.* *Int. J. Cancer*, 119: 477-483, 2006.
2. Nakamura T, Sakai K, Nakamura T, Matsumoto K. *Hepatocyte growth factor twenty years on: much more than a growth factor.* *J. Gastroenterol. Hepatol.*, 26: 188-202, 2011.
3. Sakai K, Nakamura T, Kinoshita T, Nakamura T, Matsumoto K. *HGF-antagonists: structure, activities, and anti-cancer approach.* *Current Signal Transduction Therapy*, 6: 191-199, 2011.



Prof. Xin Hu, Ph.D.

Junior Principal Investigator Breast Cancer Institute
Shanghai Cancer Center, Fudan University

Multiple Roles of the BRCA1 A Complex: From DNA Damage Repair to Mammary Duct Morphogenesis

Abstract:

Breast cancer is a malignant tumor that develops from an uncontrolled growth of mammary cells. Women with inherited genetic mutations in BRCA1 (Breast cancer type susceptibility 1 gene) have a high risk for developing breast cancer. The role of BRCA1 in DNA damage repair and cell cycle checkpoint regulation is at least partially mediated by different BRCA1 associated complexes. We are interesting in a new BRCA1 associated complex, BRCA1-A complex, which functions as a key adaptor for recruitment of BRCA1 to the DNA damage site via K63 ubiquitin signaling and plays an important role in G2/M checkpoint control. The BRCA1 A-complex contains at least five components, including Abraxas, Rap80, BRE, Brc36 and NBA1. Our work is to investigate the role of each player in the DNA damage repair signaling pathways as well as in its role in cancer progression.

We identified that Rap80 possesses a SUMO-interacting motif (SIM), capable of binding specifically to SUMO2/3 conjugates, and forms a tandem SIM-UIM-UIM motif at its N-terminus. Both the SIM and UIM (Ubiquitin-interacting motif) domains are required for efficient recruitment of Rap80 to DSBs immediately after damage and confer cellular resistance to ionizing radiation. Our findings

propose a model in which SUMO and Ub modification is coordinated to recruit Rap80 and BRCA1 to DNA damage sites.

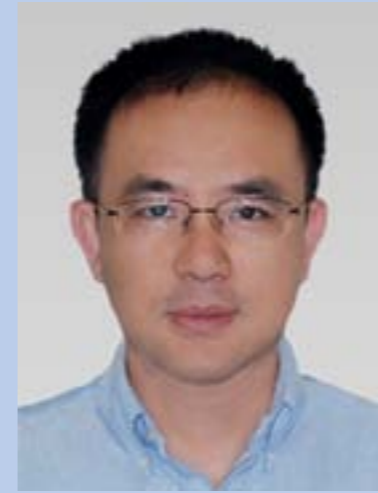
In addition, we revealed that the other two components in A-complex, NBA1 and BRE, are critical for maintaining the integrity of BRCA1 A-complex. We provided evidence that NBA1 interacts with BRE through a C-terminal conserved motif of the NBA1 protein and a C-terminal UEV domain of the BRE protein. Furthermore, the NBA1-BRE interaction is required for cellular resistance to ionizing irradiation and Brca1's recruitment to the DNA damage site. Together, these studies reveal critical interactions required for the formation and function of Brca1 A-complex.

Currently, we are interested in understanding the broader roles of BRCA1 A-complex in modulating in a variety of biological processes and disease models, with the focus on mammary duct morphogenesis and breast cancer carcinogenesis. We will employ a combination of approaches including conventional biochemistry, molecular and cellular biology as well as the cellular differentiation technology to address these questions. Our long-term goal is to understand how disruption of the mammary duct differentiation leads to breast cancer development.



Prof. Hiroshi Sato

Director, Division of Molecular Virology and Oncology
Kanazawa University Cancer Research Institute, Japan



Prof. Weiguo Hu, M.D., Ph.D.

Cancer Research Institute
Shanghai Cancer Center, Fudan University

Roles of Membrane-Type Matrix Metalloproteinase-1 in Tumor Invasion

Abstract:

Throughout the process of tumor metastasis, microenvironment surrounding tumors regulates tumor cell migration, proliferation and survival. Modification of extracellular matrix (ECM), whose major components are collagen, fibronectin and so on, is one of initial steps for tumor invasion and metastasis. Matrix metalloproteinases (MMPs) may play important roles in it. In 1994 we identified first membrane-type MMP (MT1-MMP) as an activator of MMP-2 (1). Among 23 human MMPs so far reported, MT1-MMP is one of the most attractive candidates. Although MT1-MMP was first identified as an activator of MMP-2, later its multi functions at cell-ECM interface were demonstrated to contribute to malignant phenotype of tumor cells. A lot of molecules have already been identified as substrates for MT1-MMP, which are relevant to tumor malignancy. They are ECM components (2), cell surface receptors e.g. CD44 and syndecan-1(3), and small ligand molecules e.g. KiSS-1/metastin (4).

Collagen matrix acts as physical barrier for tumor-cell invasion, but at the same time it provides cells with various signals for growth, survival, differentiation, migration and so on. Extra-cellular signal regulated kinase (ERK), which is the central molecule to transduce these signals, is activated in cells cultured in type I collagen matrix or on collagen

sheet through interaction with integrins. However, sustained activation of ERK requires turnover of focal adhesions, where integrins interact with ECM. Degradation of ECM at focal adhesions accelerates the turnover, in which MT1-MMP plays a central role (5). Thus, inhibition of MT1-MMP reduces not only tumor cell invasion/migration but also cell proliferation/survival of tumor cells in collagen matrix. We re-evaluated the pathological significance of MMP-2-activation function of MT1-MMP (6). Another substrate of MT1-MMP, which we are most interested in at the moment, is a membrane-type serine protease inhibitor Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) (7). An understanding of the functions of MT1-MMP could supply clues for developing novel therapeutic strategies targeting MT1-MMP.

References:

1. Sato H. *et al.*, *Nature* 1994; 370: 61–65.
2. Li Y. *et al.*, *Cancer Res.*, 2004; 64: 7058-7064.
3. Endo K. *et al.*, *J. Biol. Chem.* 2003; 278: 40764–70.
4. Takino T. *et al.*, *Oncogene* 2003; 22: 4617–26.
5. Takino T. *et al.*, *Cancer Res.* 2007; 67: 11621-9.
6. Nishida Y. *et al.*, *Cancer Res.* 2008; 68: 9096-114.
7. Domoto T. *et al.*, *Cancer Sci.* 2012; 103: 448-454.

CD59 Confers Resistance to Antibody-Based Therapy on Cancer Cells

Abstract:

Breast cancer is a malignant tumor that develops from an uncontrolled growth of mammary cells. Women with inherited genetic mutations in BRCA1 (Breast cancer type susceptibility 1 gene) have a high risk for developing breast cancer. The role of BRCA1 in DNA damage repair and cell cycle checkpoint regulation is at least partially mediated by different BRCA1 associated complexes. We are interesting in a new BRCA1 associated complex, BRCA1-A complex, which functions as a key adaptor for recruitment of BRCA1 to the DNA damage site via K63 ubiquitin signaling and plays an important role in G2/M checkpoint control. The BRCA1 A-complex contains at least five components, including Abraxas, Rap80, BRE, Brcc36 and NBA1. Our work is to investigate the role of each player in the DNA damage repair signaling pathways as well as in its role in cancer progression.

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a model in which SUMO and Ub modification is coordinated to recruit Rap80 and BRCA1 to DNA damage sites.

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Currently, we are interested in understanding the broader roles of BRCA1 A-complex in modulating in a variety of biological processes and disease models, with the focus on mammary duct morphogenesis and breast cancer carcinogenesis. We will employ a combination of approaches including conventional biochemistry, molecular and cellular biology as well as the cellular differentiation technology to address these questions. Our long-term goal is to understand how disruption of the mammary duct differentiation leads to breast cancer development.



Prof. Seiji Yano

Director, Division of Medical Oncology
Kanazawa University Cancer Research Institute, Japan

Molecular Targeted Therapy For Lung Cancer

Abstract:

Lung cancer is the leading cause of malignancy related death worldwide, including China and Japan. Recent advances in molecular biology have led to the identification of new molecular targets, such as mutations in EGFR and rearrangements of ALK, ROS-1, and RET, in lung adenocarcinoma. Dramatic response has been achieved with EGFR inhibitors and an ALK inhibitor in lung cancer expressing corresponding targets. However, cancer cells acquire resistance to these drugs and cause recurrence. Known major mechanisms for resistance to molecular targeted drugs include gatekeeper mutations in the target gene and activation of bypass survival signal via receptors other than the target

receptors. The latter mechanism can involve receptor gene amplification and ligand-triggered receptor activation as well. For example, HGF, the ligand of a tyrosine kinase receptor Met, activates Met and the downstream PI3K/Akt pathway and triggers resistance to EGFR inhibitors in EGFR mutant cancer cells. Moreover, EGFR ligands activate EGFR and downstream pathways and trigger resistance to ALK inhibitor in EML4-ALK cancer cells. These observations indicate that signals from oncogenic driver and ligand-triggered bypass signals must be simultaneously blocked to avoid the resistance. This talk will focus on new molecular targets and molecular mechanisms of resistance to molecular targeted drugs in lung cancer.



Prof. Menghong Sun, M.D., Ph.D.

Tissue Bank, Dept Pathology
Shanghai Cancer Center, Fudan University

Cancer Center Tissue Bank Management

Abstract:

Disease based sample procurement is of important for Tissue Banks in Cancer Centers affiliated to Universities, in order to provide high quality samples for translational medicine and personalized medicine. A number of aspects should be taken into account including ethics/informed consent, stakeholders, patient confidential, financial support and tissue bank recovery

etc. Quality is a key issue in biobanking activities. The results derived from studies based on bad quality samples will affect the whole scientific society. It would take a long time to eliminate the influence from the wrong results and the deriving interpretation. In this abstract we would discuss the quality control at RNA and protein level to attract attention from both biobank staff and scientists.



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