臺北醫學大學
TAIPEI MEDICAL UNIVERSITY

2022國際癌症研究研討會
表觀遺傳學、免疫檢查點與臨床治療

2022 International Conference on Cancer Research
Epigenetics, Immune Checkpoint, and Clinical Therapies

指導單位：科技部
Supervised by MOST

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Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare
臺北醫學大學 臺北癌症中心
Taipei Cancer Center, TMU

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Welcome Letter

Dear colleagues,

We are delighted to welcome you to the international conference of **2022 International Conference on Cancer Research: Epigenetics, Immune Checkpoint, and Clinical Therapies** held June 16-17, 2022, in the Taipei Medical University, Taipei, Taiwan.

As one of the series events to celebrate the 62nd anniversary of Taipei Medical University, this specialized conference aims to include recent advances from basic to clinical science on cancer research. We invite international experts in these areas to present their research discoveries and clinical expertise. Specifically, this conference is constituted by three themes: (1) Epigenetics, (2) Immune Checkpoint, and (3) Clinical Therapies. There is also a poster session for more scientists to share their research work.

Welcome to Taipei Medical University and we hope you will enjoy this meeting!

Sincerely,

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Taipei Medical University

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Taipei Medical University

Committee Chair
Han-Pin Kuo, MD, PhD
Dean, College of Medicine
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TMU Taipei Cancer Center

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Schedule at a Glance

Day 1	June 16, Thursday	
08:00~16:00	**Registration**	**16F Lobby, International Conference Hall (ICH)**
08:00~09:30	**Poster Set-up**	
09:30~09:50	**Opening Remarks**	**16F ICH**
	Wen-Chang Chang, Ph.D. (張文昌教授 臺北醫學大學董事長/中央研究院院士) *Chairman of Taipei Medical University Board and Academician of Academia Sinica (Taiwan)* **Chien-Huang Lin, Ph.D.** (林建煌教授 臺北醫學大學校長) *President and Professor of Taipei Medical University (Taiwan)*	
09:50~10:00	**Group Photography**	**16F ICH**
	Keynote Speech	**16F ICH**
	Moderator: Ruei-Ming Chen, Ph.D. (陳瑞明 教授/醫學科學研究所所長) *Professor & Director, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University (Taiwan)*	
10:00~10:30	**Lu Q. Le, M.D., Ph.D.** *Professorship in Dermatology, Department of Dermatology, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center (USA)* ***NF1* loss impairs stem cell differentiation to promote tumorigenesis**	
10:30~10:40	**Q&A**	
10:40~11:00	**Coffee Break**	**16F Lobby, ICH**
	Keynote Speech	**16F ICH**
	Moderator: Joen-Rong Sheu, Ph.D. (許準榕 教授/醫學院副院長) *Professor, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University (Taiwan)*	
11:00~11:30	**Keith Syson Chan, Ph.D.** *Principal Investigator, Cedars-Sinai Medical Center (Los Angeles, USA)* **Exploiting cell death-induced immunogenicity to enhance response to immune checkpoint inhibitors**	
11:30~11:40	**Q&A**	
11:40~12:00	**Poster Section**	**16F Lobby ICH**
12:00~13:00	**Lunch**	

Session I: Epigenetics **16F ICH**

Moderator: Jia-Yi Wang, Ph.D. (王家儀 名譽教授)

Professor, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University (Taiwan)

13:00~13:25 **Hung-Cheng Lai, M.D., Ph.D.** (賴鴻政 教授/雙和醫院主治醫師)

Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, and Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei Medical University (Taiwan)

Immunotherapy of ovarian cancer: current status and future perspective immunotherapy

13:25~13:35 **Q&A**

13:35~14:00 **Hsing-Chen Tsai, M.D., Ph.D.** (蔡幸真 助理教授/臺大醫院主治醫師)

Assistant Professor, Graduate Institute of Toxicology, National Taiwan University; Department of Internal Medicine, National Taiwan University Hospital (Taiwan)

Rewiring the circuits: modulating the cancer epigenome for effective cancer immunotherapy

14:00~14:10 **Q&A**

14:10~14:35 **Chung-Ping Liao, Ph.D.** (廖崇斌 副教授)

Associate Professor, Graduate Institute of Medical Sciences, Taipei Medical University (Taiwan)

Histone methylation status determines malignant peripheral nerve sheath tumor vulnerability

14:35~14:45 **Q&A**

14:45~15:10 **Tsai-Tsen Liao, Ph.D.** (廖彩岑 助理教授)

Assistant Professor, Graduate Institute of Medical Sciences, Taipei Medical University (Taiwan)

Chromatin remodeling in cancer: mechanisms and functional impact

15:10~15:20 **Q&A**

15:20~15:40 **Coffee Break** **16F Lobby ICH**

15:20~15:40 **Poster Section** **16F Lobby ICH**

Session II: Immune Checkpoints **16F ICH**

Moderator: Wen-Sen Lee, Ph.D. (李文森 名譽教授)

Professor, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University (Taiwan)

15:40~16:05 **Shuen-Iu Hung, Ph.D.** (洪舜郁 教授/長庚醫院癌症疫苗暨免疫細胞治療核心實驗室主任)

Professor, Cancer Vaccine & Immune Cell Therapy Core Lab, Department of Medical Research, Chang Gung Memorial Hospital (Taiwan)

Targeting neoantigens for precision immune cell therapy against cancers

16:05~16:15 **Q&A**

16:15~16:40 **Chia-Wei Li, Ph.D.** (李家偉 助研究員)

Assistant Research Fellow, Institute of Biomedical Sciences, Academia Sinica (Taiwan)

Targeting glycosylated PD-1 induces potent anti-tumor immunity

16:40~16:50 **Q&A**

16:50~17:15 **Yu-Cheng Lee, Ph.D.** (李育誠 助理教授)

Assistant Professor, Graduate Institute of Medical Sciences, Taipei Medical University (Taiwan)

RNF144A deficiency promotes PD-L1 protein stabilization and carcinogen-induced bladder tumorigenesis

17:15~17:25 **Q&A**

18:00~21:00 **Banquet**

Day 2	June 17, Friday	
08:00~11:00	**Registration**	**16F Lobby, International Conference Hall (ICH)**
	Session III: Clinical Therapies	**16F ICH**
	Moderator: Chun-Jen Huang, M.D., Ph.D. (黃俊仁 教授/醫學院副院長/萬芳醫學中心研究副院長) *Professor, Vice dean of College of Medicine; Deputy Superintendent of Wan Fang Medical Center (Taiwan)*	
09:00~09:25	**Muh-Hwa Yang, M.D., Ph.D.** (楊慕華 教授/陽明交大副校長/台北榮總主治醫師) *Senior Vice President and Provost of National Yang Ming Chiao Tung University (Taiwan)* **Microenvironmental evolution during cancer progression**	
09:25~09:35	**Q&A**	
09:35~10:00	**Kuo-Shyan Lin, Ph.D.** *Associate Professor, Department of Radiology, University of British Columbia; Senior Scientist, Department of Functional Imaging, BC Cancer (Canada)* **Discovery of novel pharmacophores to reduce kidney and salivary gland uptake of PSMA-targeting radiopharmaceuticals**	
10:00~10:10	**Q&A**	
10:10~10:30	**Coffee Break**	**16F Lobby, ICH**
10:30~10:55	**Tai-Tong Wong, M.D.** (黃棣棟 教授/北醫附醫主治醫師) *Professor, Taipei Medical University Hospital, Taipei Medical University (Taiwan)* **CNS germ cell tumors in children and adolescents: The experience in a cohort series in Taiwan and their clinical-molecular correlation**	
10:55~11:05	**Q&A**	
11:05~11:30	**J. Timothy Qiu, M.D., Ph.D.** (邱德生 教授/細胞治療學程主任) *Professor, International Ph.D. Program for Cell Therapy and Regeneration Medicine, College of Medicine; Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei Medical University (Taiwan)* **Immune checkpoint inhibitor and cell therapy in gynecological cancers**	
11:30~11:40	**Q&A**	

	Awards of Poster Section Winners and Closing Remarks	**16F ICH**
11:40~12:00	**Han-Pin Kuo, M.D., Ph.D.** (郭漢彬 教授/醫學院院長) *Professor & Dean, College of Medicine, Taipei Medical University (Taiwan)*	

Conference Organization
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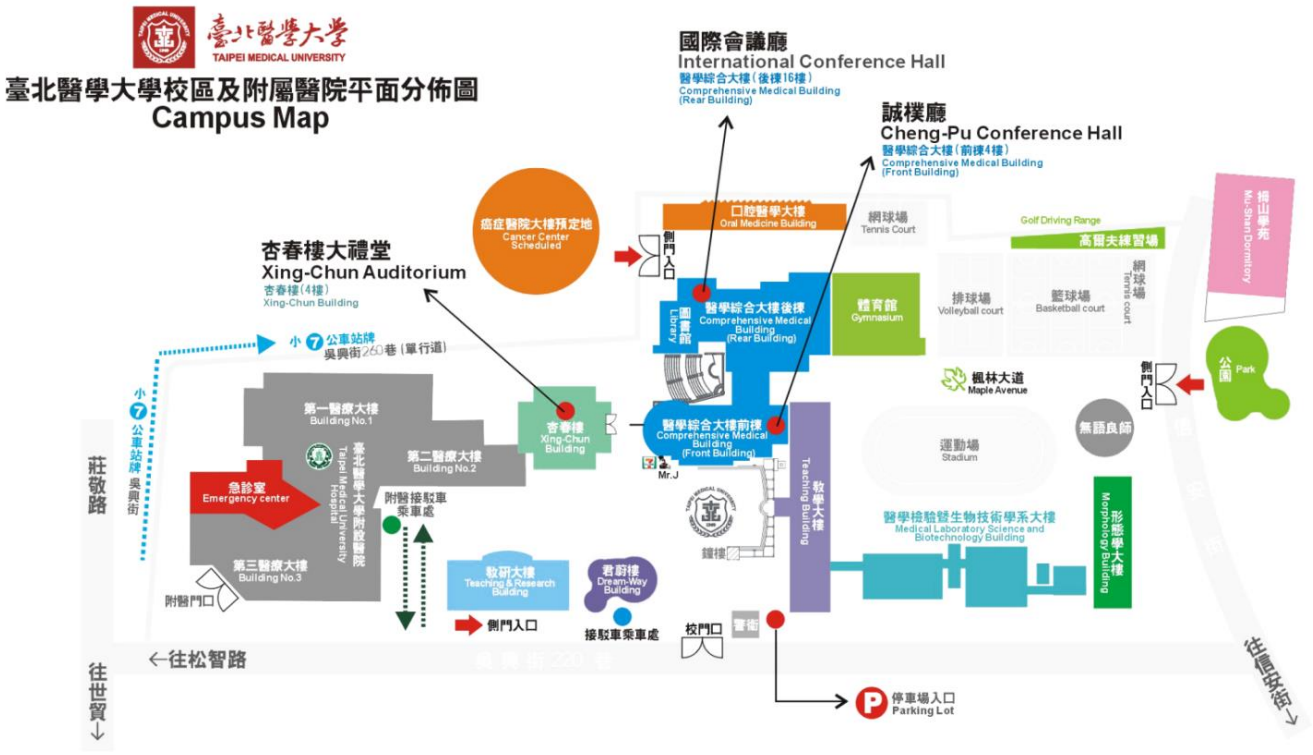
Map Guide

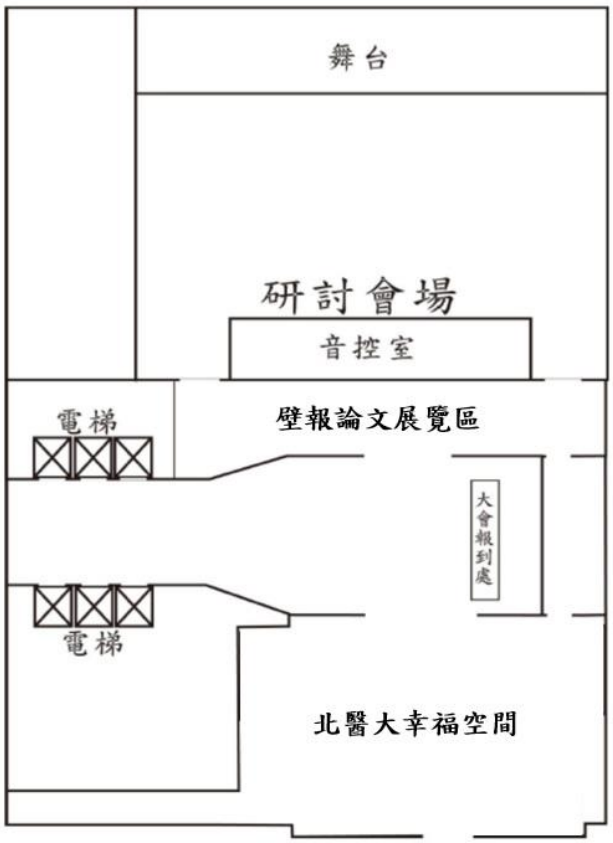
會場指南



Exhibition Floor Plan

醫學綜合大樓十六樓國際會議廳

16F International Conference Hall



- 研討會開幕及演講會場
- 研討會報到處
- 壁報論文展覽區

Wireless Setting

請點選申請訪客帳號

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Invited Speakers

Lu Q. Le, M.D., Ph.D.

Thomas L. Shield, M.D. Endowed Professorship in Dermatology
Residency Program Associate Director for the Physician-Scientist Track
Department of Dermatology
Simmons Comprehensive Cancer Center
The University of Texas Southwestern Medical Center

Publications

- Somatilaka BN, Sadek A, McKay RM, Le LQ*. Malignant peripheral nerve sheath tumor: models, biology, and translation. Oncogene. 2022 Apr;41(17):2405-2421.
- Mo J, Moye SL, McKay RM, Le LQ*. Neurofibromin and suppression of tumorigenesis: beyond the GAP. Oncogene. 2022 Feb;41(9):1235-1251.
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NF1 loss impairs stem cell differentiation to promote tumorigenesis

Juan Mo [1], Tracey Shipman [1], and Lu Q. Le [1,2,3,4]

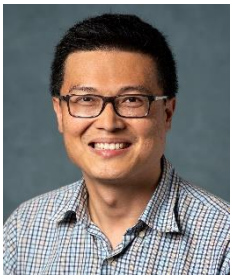
[1] Department of Dermatology, [2] O'Donnell Brain Institute, [3] Simmons Comprehensive Cancer Center, [4] Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

Neurofibromas are Schwann cell tumors that affect most individuals with Neurofibromatosis Type 1 (NF1). The complexity of neurofibroma biology stems from its heterogeneity at multiple levels including genetic, spatial involvement, temporal development, and cellular compositions. Despite multiple gaps remain in our knowledge of the associated pathogenesis, significant inroads have been made into neurofibroma understanding in recent years, including intrinsic and extrinsic factors that regulate its growth and progression into malignancy. While the development of neurofibroma involves a complex interplay between intra- and intercellular components, tumorigenesis begins at the molecular level with *NF1* LOH that activates the RAS pathway. This RAS/MAPK pathway activation affects not only cellular proliferation but also Schwann cell differentiation by inducing a persistent stem-like state to expand the pool of progenitors required to initiate tumor formation, indicating that in addition to regulating MAPK-mediated cell growth, NF1 loss also alters Schwann cell differentiation to promote neurofibroma development. This knowledge combines with translational and relevant humanized models currently being developed will provide unique opportunities to unravel its biology to accelerate the development of prevention and new treatment strategies for NF1-associated neoplasms.

Keywords: Neurofibromatosis, NF1, Neurofiroma, RAS, MAPK pathway

Keith Syson Chan, Ph.D.



Professor, Academic Pathology, Cedars-Sinai Medical Center, USA
Adjunct faculty, Department of Molecular & Cellule Biology, Baylor College of Medicine, USA

Publications

- Nikolos F, Hayashi K, Hoi XP, Alonzo ME, Mo Q, Kasabyan A, Furuya H, Trepel J, Di Vizio D, Guarnerio J, Theodorescu D, Rosser C, Apolo A, Galsky M, Chan KS*. Cell death-induced immunogenicity enhances chemoimmunotherapeutic response by converting immune-excluded into T-cell inflamed bladder tumors. Nat Commun. 2022 Mar 28;13(1):1487.
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Exploiting cell death-induced immunogenicity to enhance response to immune checkpoint inhibitors

Keith Syson Chan

Department of Pathology and Laboratory Medicine, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, 90048, USA

Abstract

Most anticancer therapy designate programmed cell death as the therapeutic end goal. Emerging studies, including those of ours, revealed cell death induced biology paradoxically impacts therapy response [*Nature* 517, 209-213 (2015); *Nat Commun* 11, 6299 (2020), *Nat Commun* 13, 1487 (2022)]. The recent failure of chemoimmunotherapy (i.e., the combination of standard chemotherapy and immune checkpoint inhibitor) in two Phase 3 clinical trials—IMvigor130 and KEYNOTE-361—poses a new clinical challenge for the treatment of advanced bladder cancer patients. Here, we evaluated the immunogenic cell death paradigm in modulating chemoimmunotherapy response. The current molecular hallmark of immunogenic cell death features the extracellular release of "danger" signals or "damage-associated molecular patterns (DAMPs)" from dying cancer cells, which activates pattern recognition receptors on dendritic cells rendering their maturation to prime an effective CD8+ T cell response. However, our recent data indicated despite gemcitabine chemotherapy inducing the release of hallmark immunostimulatory DAMPs (e.g., calreticulin, HSP70, and HMGB1), it was unable to induce immunogenic cell death in the classical vaccination assay in vivo. Mechanistic studies revealed gemcitabine concurrently triggers prostaglandin E2 release, which functions as an "inhibitory" DAMP to counterpoise the adjuvanticity of immunostimulatory DAMPs; thereby, hindering dendritic cell maturation. Pharmacological blockade of PGE2 biosynthesis and its release favored CD103+ dendritic cell activation to prime a Tc1-polarized CD8+ T cell response. Subsequent CD8 antibody-mediated depletion experiments confirmed that the resulting tumor-infiltrating CD8+ T cells were tumoricidal. Moreover, removal of the inhibitory DAMP converted an otherwise "immune-excluded" landscape into a more "T-cell-inflamed" (or intraepithelial-infiltrating) tumor microenvironment (TME). Intriguingly, this "inhibitory DAMP blockade" strategy synergized with chemotherapy and sensitized syngeneic bladder tumors to respond towards chemoimmunotherapy. Collectively, these findings challenge the current dogma by highlighting an intricate balance between immunostimulatory and inhibitory DAMPs within the local TME to determine the outcome of drug-induced immunogenic cell death. These preclinical finding poses a compelling rationale to evaluate inhibitory DAMP blockade in combination with chemoimmunotherapy for future clinical trials.

Keywords: Bladder cancer, Immune checkpoint, DAMPs, PGE2, Immunogenic cell death

Hung-Cheng Lai, M.D., Ph.D. 賴鴻政 教授

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Consultant doctor, Shuang Ho Hospital, Taipei Medical University, Taiwan

Publications

- Chen CW, Huang RL, Do AQ, Wang HC, Lee YX, Wang CW, Hsieh CC, Tzeng CR, Hu YM, Chen CH, Weng YC, Su PH, Chen LY, Lai HC*. Genome-wide analysis of cervical secretions obtained during embryo transfer reveals the association between deoxyribonucleic acid methylation and pregnancy outcomes. F S Sci. 2022 Feb;3(1):74-83.
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Immunotherapy of ovarian cancer: current status and future perspective immunotherapy

Hung-Cheng Lai

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Abstract

Immunotherapies, including immune checkpoint inhibitors (ICIs) and immune cell therapies (ICTs), have shown unprecedented durable responses. However, in ovarian cancer, the responses to immune checkpoint inhibitors and immune cell therapies are limited. PD-L1 is expressed in 28% to 40% of patients with ovarian cancer. However, only a minority of patients with ovarian cancer respond to ICIs. 8% of patients responded to treatment, and subgroup analysis in ovarian clear cell carcinoma patients showed a 19.0% response rate. Combining ICIs with anti-angiogenic agents can exert a synergistic anti-tumor effect in many cancers, including ovarian cancer. However, a further clinical trial is needed.

ICTs, including the adoptive transfer of tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, or engineered immune components such as chimeric antigen receptor (CAR) constructs and engineered T-cell receptors, have demonstrated clinical benefit in cancer patients. Nevertheless, ovarian cancer shows limited anti-tumor activity in early-phase clinical trials. Until 2018, dendritic cell-based immunotherapy pulsed with tumor antigen showed an encouraging result.

In contrast to other cancers, ovarian cancer shows slow progress in ICIs and ICTs due to high regulatory T cells, high MDSCs, lack of tumor-infiltrating T cells, and high immunosuppression in the tumor microenvironment. Further investigation with new technology may shed new light on improving ovarian cancer immunotherapy.

Keywords: Immunotherapy, immune checkpoint inhibitors (ICIs), immune cell therapies (ICTs), T cells

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Rewiring the circuits: modulating the cancer epigenome for effective cancer immunotherapy

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Abstract

Cancer immunotherapy has revolutionized current practices of cancer treatment. Nevertheless, only a small subset of patients benefit from immune checkpoint blockade therapy. Epigenetic therapy such as DNA methyltransferase inhibitors (DNMTis) may modulate immunogenicity of cancer cells through upregulation of major histocompatibility complexes (MHC), cancer-testes antigens, and viral defense genes, thereby enhancing MHC-dependent immunotherapy such as immune checkpoint inhibitors. Nevertheless, whether and how epigenetic therapy may affect the interaction between cancer and immune cells in an MHC-independent manner remains unclear. Through quantitative surface proteomics, we discovered that DNMTis upregulate surface molecules on cancer cells related to γδ T cell activation. γδ T cells are a distinct subgroup of T cells that bridge the innate and adaptive immune systems and exert anti-cancer immunity in an MHC-unrestricted manner. We successfully established a clinical-grade protocol for ex vivo expansion of V δ 1 cells, a more potent subtype of γδ cells. We showed that DNMTi treatment of human lung cancer potentiates tumor lysis by ex vivo-expanded Vδ1-enriched γδ T cells. Mechanistically, DNMTi enhances immune synapse formation and mediates cytoskeletal reorganization via coordinated alterations of DNA methylation and chromatin accessibility. Genetic depletion of adhesion molecules or pharmacological inhibition of actin polymerization disrupts the strengthened immune synapses and abolishes the potentiating effect of DNMTi. Clinically, the DNMTi-associated cytoskeleton signature stratifies lung cancer patients prognostically. Thus, our results demonstrate that epigenetic mechanisms are crucial for cytoskeletal remodeling and cancer-immune interaction, which paves the way to developing novel therapeutic options for epigenetic-based cancer immunotherapy.

Keywords: DNA methyltransferase inhibitors (DNMTis), Lung cancer, Immune synapse, γδ T cells, Adoptive cell therapy

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Histone methylation status determines malignant peripheral nerve sheath tumor vulnerability

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Abstract

Neurofibromatosis type 1 (NF1) is a tumor predisposition genetic syndrome caused by *NF1* mutation. One of the common cancers targeting NF1 patient is malignant peripheral nerve sheath tumor (MPNST), which is a highly dangerous cancer lacking effective treatments in the clinic. The genetic landscape of MPNST usually includes the mutations of *NF1* together with at least one of the tumor suppressors of *P53*, *PTEN*, *SUZ12*, *EED*, or *CDKN2A*. A key tumorigenic mechanism inducing the development of MPNST is the epigenetic switch on histone H3. Mutations on SUZ12/EED (components of PRC2) result in the epigenetic modification on H3K27 residue from methylation to acetylation, a critical driver for MPNST proliferation. In this study, we investigated other epigenetic regulators and found that the lysine-specific demethylase 1 (LSD1) is upregulated in MPNST cells as compared to normal Schwann cells. LSD1 is best known to regulate gene expressions by demethylating H3K4 and H3K9 residues. Knockdown of LSD1 significantly impedes MPNST viability. By RNA-sequencing analysis and qPCR conformation, we found that TXNIP, a redox metabolism regulator, is upregulated in response to LSD1 knockdown. Induction of TXNIP increases cellular ROS levels, causing oxidative stress. Pharmacological block of LSD1 demethylase activity by a new class of inhibitor SP2577 potently arrests MPNST cell cycle at G1 phase and induces apoptotic death. Importantly, SP2577-treated MPNST cells showed significantly increases on histone H3 methylations on multiple lysine sites, including H3K4, H3K9, H3K27, H3K36, and H3K79. In summary, our data suggested that the epigenetic status of histone 3 lysine methylation is a determining factor for MPNST survival and vulnerability, and this balance is likely controlled by the TXNIP-mediated oxidative stress homeostasis.

Keywords: Malignant peripheral nerve sheath tumor (MPNST), Neurofibromatosis type 1 (NF1), Lysine-specific demethylase 1 (LSD1), Thioredoxin-interacting protein (TXNIP), Reactive oxygen species (ROS)

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Chromatin remodeling in cancer: mechanisms and functional impact

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Abstract

Cancer stem cells (CSCs) are a small population of heterogeneous tumors with the ability to self-renew, progress, tumor initiation, and resist chemotherapy, which were regarded as the seeds of cancer initiation. Moreover, the increase of PD-L1 was also shown in the cancer stem-like cells and CSCs that contribute to CSC immune evasion and maintain the tumorigenic process. Therefore, CSCs are more resistant to immunological control compared with non-CSCs, and cancer immunosurveillance enriches a subpopulation of cancer cells with stem-like properties. Furthermore, killing cancer stem cells would free the niche and allow differentiated tumor cells to fill the space to become cancer stem cells. Therefore, instead of targeting cancer stem cells, we address elucidating the role of the critical factor, ARID3B, that dedifferentiation of differentiated tumor cells to acquire the stemness property and select the useful inhibitors. Our previous studies indicated that ARID3B regulates stemness genes is context-dependent through the histone demethylation pathway. Moreover, the results indicated that the ARID3B-regulated signature was significantly associated with an advanced stage and recurrence of CRC. In CRC, ARID3B can provide an alternative non-canonical pathway to activate the NOTCH pathway downstream target through KDM4C and activate the expression of PD-L1. The enrichment of PD-L1 in the ARID3B+ CSC can trigger the immune evasion of the CRCSCs under immune surveillance. Therefore, unraveling how cancer cells acquire stem-like properties may allow clinicians to develop more approaches to interfere with these processes and ultimately improve cancer treatment.

Keywords: KDM4C, Chromatin modification, ARID3B, PD-L1

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Targeting neoantigens for precision immune cell therapy against cancers

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Abstract

Targeting tumor-specific antigens, also known as neoantigens, have been considered as ideal targets for cancer immunotherapy. Neoantigens could be presented by the MHC molecules and then recognized by the T cell receptors (TCR) to induce the adaptive immunity, and trigger tumor-specific cytotoxic T cell killing. Targeting neoantigens for precision immunotherapy against cancers is becoming an emerging field for tumor treatment. The efficacy of neoantigens presentation to the immune system however may vary with the applied technologies as well as the patient populations due to the tumor heterogeneity, diversity of cancer somatic mutations, and MHC polymorphisms of individuals. Different approaches targeting neoantigens, including cancer vaccines and adoptive T cell therapy have been developing. We aim to develop personalized neoantigen-based T cell therapy for treating cancers. We enroll patients with advanced cancers in a clinical trial to evaluate the dosage, safety, tolerability, and efficacy of neoantigen-expanded autologous immune cell therapy. In the clinical setting, we investigate the patient-specific tumor somatic mutations to generate “personalized cancer vaccine”, and expand neoantigen-targeted T cells for cell therapy. Our data suggest that neoantigen-driven T cell therapy could lead to robust anti-tumor response and effective against the aggressive cancer even with dynamic change of tumor genome.

Keywords: Cell therapy, Neoantigens, Immunotherapy

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Targeting glycosylated PD-1 induces potent anti-tumor immunity

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Abstract

Immunotherapy targeting programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoints represents a breakthrough in cancer treatment. PD-1 is an inhibitory receptor expressed on the surface of activated T cells that dampens T-cell receptor (TCR)/CD28 signaling by engaging with its ligand PD-L1 expressed on cancer cells. We found that PD-1 is extensively N-glycosylated in T cells, and the intensities of its specific glycoforms are altered upon TCR activation. Poly-LacNac glycosylation is critical for maintaining PD-1 protein stability, cell surface localization, and is enriched in tumor-infiltrating lymphocytes (TILs). A monoclonal antibody that specifically targets glycosylated PD-1, STM418, exhibits a higher binding affinity to PD-1 than FDA-approved PD-1 antibodies, potently inhibits PD-L1/PD-1 binding, and exhibits tumor specificity. We developed a novel antibody-drug conjugate (ADC) by coupling a small molecule inhibitor to the STM418 antibody to epigenetically reprogram effector T cell into long-lived memory T cells. We found that post-effector de novo DNA methylation promotes terminal T cell exhaustion. Thus, blocking de novo methylation enhances antigen sensitive, long-lived, and potent T cell immunity against triple-negative breast cancer recurrence and metastasis.

Keywords: Breast cancer, PD-1, Antibody drug conjugate (ADC)

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RNF144A deficiency promotes PD-L1 protein stabilization and carcinogen-induced bladder tumorigenesis

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Abstract

RNF144A is a DNA damage-induced E3 ubiquitin ligase that targets proteins involved in genome instability for degradation, e.g., DNA-PKcs and BMI1. *RNF144A*is frequently mutated or epigenetically silenced in cancer, providing the rationale to evaluate RNF144A loss of function in tumorigenesis. Here we report that RNF144A-deficient mice are more prone to the development of bladder tumors upon carcinogen exposure. In addition to DNA-PKcs and BMI1, we identify the immune checkpoint protein PD-L1 as a novel degradation target of RNF144A, since these proteins are expressed at higher levels in *Rnf144a* KO tumors. RNF144A interacts with PD-L1 in the plasma membrane and intracellular vesicles and promotes poly-ubiquitination and degradation of PD-L1. Therefore, *Rnf144a* KO stabilizes PD-L1 and leads to a reduction of tumor-infiltrating $CD8^+$ T cell populations in the BBN-induced bladder tumors. The bladder tumors developed in WT and *Rnf144a* KO mice primarily express CK5 and CK14, markers of basal cancer subtype, as expected in BBN-induced bladder tumors. Intriguingly, the *Rnf144a* KO tumors also express GATA3, a marker for the luminal subtype, suggesting that RNF144A loss of function promotes features of cellular differentiation. Such differentiation features in *Rnf144a* KO tumors likely result from a decrease of EGFR expression, consistent with the reported role of RNF144A in maintaining EGFR expression. In summary, for the first time our study demonstrates the *in vivo* tumor suppressor activity of RNF144A upon carcinogenic insult. Loss of RNF144A promotes the expression of DNA-PKcs, BMI1 and PD-L1, likely contributing to the carcinogen-induced bladder tumorigenesis.

Keywords: RNF144A, Bladder cancer, BMI1, DNA-PKcs, PD-L1

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Microenvironmental evolution during cancer progression

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Abstract

The communication and mutual influences between cancer cells and immune cells have been well established. However, understanding about the dynamic interaction between cancer cells and microenvironmental immune cells during cancer progression is relatively limited. The epithelial-mesenchymal transition (EMT) has been recognized as a major mechanism responsible for cancer progression. Here, we present the dynamic interplay between the EMT-undergoing cancer cells and immune cells during cancer progression. Acetylation of the EMT transcriptional factor Snail in cancer cells promotes the recruitment of tumor-associated macrophages by secreting CCL2 and CCL5. Furthermore, the miR-21-abundant exosomes secreted from Snail-expressing cancer cells polarize tumor-associated macrophages (TAMs) toward a M2-like phenotype and suppress NLRP3 inflammasome activities to attenuate therapy-induced immune responses. Cancer stem cells secreted exosomal triphosphate RNAs induce the expression of IL-1β to sustain the survival of tumor-infiltrated neutrophils that facilitate tumor progression. In metastatic microenvironments, we found that TAMs secrete interleukin-35 to promote colonization of metastatic tumor cells. In summary, we found a dynamic interplay between cancer cells and microenvironmental immune cells through the secretion of cytokines / chemokines and exosomes. The bidirectional interaction facilitates late-stage progression and metastasis of tumors.

Keywords: Tumor-associated macrophages, Inflammasome, Exosome

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Discovery of novel pharmacophores to reduce kidney and salivary gland uptake of PSMA-targeting radiopharmaceuticals

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Abstract

Prostate-specific membrane antigen (PSMA)-targeting radiotherapeutic agents have been widely used in the clinic to treat metastatic prostate cancer. However, their off-target uptake in kidneys and salivary glands poses a toxicity concern and can severely affect quality of life for survivors. Recently we observed in a mouse model that monosodium glutamate pretreatment reduced uptake of ^{68}Ga-PSMA-11 in salivary glands and kidneys but had no effect on tumor uptake (Rousseau E, et al. J Nucl Med 2018; 59: 1865). This suggests that the Glu motif in the widely used Lys-urea-Glu pharmacophore might mediate the off-target uptake of PSMA-targeting radioligands. In this study, we investigated the effects of replacing Glu in the PSMA-targeting Lys-urea-Glu pharmacophore of our previously reported ^{68}Ga-HTK03041 (Kuo HT, et al. J Nucl Med 2021; 62: 521) with a close analog on the uptake of kidneys, salivary glands and PSMA-expressing LNCaP tumor xenografts. New derivatives by replacing Glu in ^{68}Ga-HTK03041 with Aad (2-aminoadipic acid, ^{68}Ga-HTK03149), Cmc (S-carboxymethylcysteine, ^{68}Ga-HTK03177), Cms (O-carboxymethylserine, ^{68}Ga-HTK03187), or (4R)-4-F-Glu (^{68}Ga-HTK04033) were synthesized and evaluated by positron emission tomography imaging and biodistribution studies at 1h post-injection in mice bearing LNCaP tumor xenografts. Compared with the high uptake of ^{68}Ga-HTK03041 in tumors (23.1 ± 6.11 %ID/g), kidneys (170 ± 26.4 %ID/g) and salivary glands (4.99 ± 0.88 %ID/g), the new derivatives showed comparable uptake values in tumors (18.3 - 24.7 %ID/g) but much lower uptake values in kidneys (2.83 - 7.76 %ID/g) and salivary glands (0.13 - 0.22 %ID/g). Our data suggest that replacing Glu in the widely used PSMA-targeting Lys-urea-Glu pharmacophore with a close analog can greatly reduce the off-target uptake in kidneys and salivary glands. The new pharmacophores, Lys-urea-Aad, Lys-urea-Cmc, Lys-urea-Cms and Lys-urea-4-F-Glu, are promising for the design of PSMA-targeting radioligands especially for radiotherapeutic agents to minimize toxicity to kidneys and salivary glands.

Keywords: Prostate cancer, Prostate-specific membrane antigen, Radioligand therapy, Positron emission tomography, Toxicity

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CNS germ cell tumors in children and adolescents: The experience in a cohort series in Taiwan and their clinical-molecular correlation

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Abstract

Primary central nervous system (CNS) GCTs present as intracranial and rarely spinal tumors. The age standardized incidence rate (ASR) per million was 4.5 in Japan (Age <15 years); 4.9 in Korea, 2.3 in USA (Age <19 years), and 2.3 (age 0-19 years) in Taiwan (registry for malignant tumor only), respectively. CNS GCTs are heterogeneous in histological types of different malignancy, locations, imaging features at diagnosis, staging status (M0-3), serum/CSF tumor markers (AFP and/or β-hCG) in secreting tumors, size, vascularity, associated hydrocephalus, and molecular status (for clinical correlation and new therapy). Clinical presentations correlate with tumor location, associated hydrocephalus, and serum/CSF titer of β-hCG. Conventional therapeutic approaches w/wo histological verification include surgical biopsy/resection, chemotherapy, radiotherapy, or the combination.

In this report, the clinical aspects of a cohort series of 326 cases of CNS GCTs (aged 0-19 years) were analyzed through the collaboration of two institutes including TMUH (1971-2019) and Taipei TMUH (2015-2021). Age-sex distribution, histopathological diagnosis and distribution of subtypes, locations, staging (M0-1, M2-3), serum markers at diagnosis, associated hydrocephalus, therapeutic approaches treatment strategies, and survivals were reviewed and analysis. Within these series, frozen tumor tissues were available in 61 cases. Blood samples were irregularity collected. RNA-Seq and DNA methylation were performed. Chromosomal aberrations, somatic mutation in a panel of 73 genes, EMT genes, TGF-β signaling, cell-type enrichment and immune cell enrichment analysis were executed. We try to correlate molecular features with clinical manifestations and outcomes between germinomas and different types of NGGCTs. Somatic mutation of JMJDIC gene (a gene associated with the risk of developing intracranial GCTs) was observed in our cohort series and will be correlated with germline mutation (ongoing). Our interest is to identify radioresistant genes in NGMGCTs for the potential of de-escalation radiotherapy in selected NGMGCTs. Tumor cell/organoid culture of germinoma and mixed GCT were achieved for this purpose.

Keywords: Central Nervous System, Germ cell tumor, Germ cell tumor, Nongerminomatous germ cell tumor, Clinical-molecular correlation

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Immune checkpoint inhibitor and cell therapy in gynecological cancers

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Abstract

Emerging data demonstrate that tumorigenesis resulting in ovarian, uterine and cervical cancers is a consequence of impaired host immune responses to cancerous cells. Leveraging the immune system through use of immune checkpoint inhibitors, therapeutic vaccine therapy and cell therapy presents a profound opportunity to revolutionize cancer treatment. This talk will encompass the role of the immune system in development of gynecologic cancers and highlight recent data regarding immunotherapy applications in ovarian, uterine and cervical cancers.

Keywords: Gynecological cancers, PD-L1, Immune checkpoint inhibitors (ICIs), Cell therapy

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Poster 1

Preclinical Assessment of a Platinum-Containing Chemotherapeutics [Dichloro(4,4'-Bis(2,2,3,3-Tetrafluoropropoxy) Methyl)-2,2'-Bipryridine) Platinum] on Triple-Negative Breast Cancers

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Abstract

Cisplatin is the most common platinum-containing chemotherapeutics in cancer therapy against various types of cancers. However, long-term exposure to cisplatin triggers drug resistance and severe side effects and limits its effectiveness and application in patients with aggressive or metastatic cancers. To unbraid this urgent topic in medicine, we developed and assessed a potential cisplatin-modified compound with better therapeutic effects and lower adverse responses in the following studies. Dichloro [4,4'-bis(2,2,3,3-tetrafluoropropoxy)methyl)-2,2'-bipryridine] platinum (TFBPC), a polyfluorinated bipyridine-modified analogue, was synthesized to enhance the amphiphilic characteristic and in vitro cytotoxicity against a panel of cisplatin-resistant human cancer cell lines, including MDA-MB-231 and MCF-7 breast cancers, COLO205 colon cancers and SK-OV-3 ovarian cancers. TFBPC successfully bound to DNA and formed DNA crosslinks that resulted in the double-strand DNA degradation, triggering the cell death program through PARP/Bax/Bcl-2 and LC3-related pathways. The results indicated the different DNA-binding patterns and cell death processes between the administrations of TFBPC and CDDP in MDA-MB-231 cells. Moreover, TFBPC significantly encouraged treatment outcomes in both animal models, a cell line-derived xenograft model (CDX) of cisplatin-resistant MDA-MB-231 cells and an orthotopic patient-derived xenograft (PDX) model of triple-negative breast cancers (TNBCs). The biopsy specimen from TFBPC-treated xenografts revealed a decrease in expressions of P53, Ki-67 and PD-L1, an increase in expression of cleaved caspase 3, and no significant pathological changes observed in hematological and biochemistry tests. Our results suggested that the platinum-containing derivative TFBPC can potentially provide an alternative chemotherapeutic option in the future for multiple patients with cisplatin-resistant cancers and triple-negative breast cancers.

Keywords: Cisplatin; Cisplatin-resistant; Cell line-derived xenograft model; Triple-negative breast cancers; Patient-derived xenograft

Poster 2

Investigating the Oncogenic Roles of a9-Nicotinic Acetylcholine Receptor Variants in Breast Cancer

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Abstract

Nicotine acetylcholine receptors (nAChRs) play an important role in the development of many cancers. When nAChRs activated by nicotine will trigger several intracellular signaling pathways that are carcinogenic. The previous study found that the main nAChRs in Taiwan women's breast cancer tissues were α5-, α9-, and α10-, and the expression of α9- was significantly higher than α5- and α10- in normal and tumor tissues. Until now, it has been proved that when single nucleotide polymorphisms (SNPs) occur within genes or in regulatory region near genes may alter the biological function of proteins and increase the risk of cancer. We hypothesized that some SNPs located in α9-nAChR gene will produce a polymorphic variant that affects the carcinogenic mechanism on breast cancer.

We previously have confirmed the presence of SNP (G/A) at 1325 bp locus by detecting α9-nAchR gene in human breast cancer, healthy human tissue and blood (n=567). In this study, we first analyzed the protein expression and genotype of α9-nAchR in different subtypes of breast cancer cell lines By gene sequencing and immunoprecipitation, we proved that this variant causes amino acid (S442N) change and affects the phosphorylation of α9-nAchR. We also found that this variant affects the protein stability of α9-nAchR and triggers different intracellular signal pathways. Therefore, we further evaluated the effect of this variant on cell behavior in α9-nAchR-S442 and -N442 overexpressed cells. The results showed that α9-nAchR-N442 overexpression significantly enhanced cell migration, invasion, stemness and malignancy in vitro. Eventually, we established two PDX-TNBC mice with two different genotypes and found that this polymorphism (S442N) may regulate the sensitivity of nicotine to affect tumor growth in vivo. Taken together, we think that this α9-nAchR polymorphism can be useful in the risk assessment and diagnosis for breast cancer patients.

Keywords: Breast cancer; Nicotine acetylcholine receptors; Single nucleotide polymorphisms

Poster 3

Effects of Knocking-Down Bradykinin B1 Receptor on Migration of Glioblastoma Multiforme Cells

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive brain tumor. Rapid migration is a typical feature of GBM cells. Bradykinin receptor B1 (BDKRB1) is bradykinin-drive calcian channel. Our previous study has shown that the bradykinin-BDKRB1 axis is involved in migration of GBM cells via activation of the MAPK-NFκB-aquaporin 4 pathway. In this study, we further aimed to evaluate the efficacy of R715, an antagonist of BDKRB1, on migration of GBM cells and the possible mechanisms. Exposure of GBM cells to R715 did not affect cell morphology and cell viability. Treatment of GBM cells with bradykinin stimulated cell migration. In contrast, pretreatment with R715 did not influence cell movement but led to a significant inhibition of bradykinin-induced migration of GBM cells. As to the mechanisms, bradykinin increased phosphorylation of ERK1/2. Pretreatment with R715 attenuated bradykinin-induced activation of ERK1/2. In addition, the bradykinin-induced augmentation of cytosolic ROCK protein in GBM cells were successively suppressed by R715. Therefore, this study demonstrated that downregulation of the BDKRB1 could inhibit the bradykinin-induced migration of GBM cells through the ERK1/2/ROCK pathways.

Keywords: Glioblastoma multiforme; Bradykinin receptor B1; Cell migration; R715; ERKs/ROCKY

Poster 4

Metformin, a Biguanide Hypoglycemic Drug, Prevention of Tumor Cell-Induced Platelet Aggregation

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Abstract

Diabetes is associated with increased risk of several cancers including colorectal cancer, endometrial cancer, prostate cancer, lung cancer, and hepatocellular carcinoma. Metformin is the most widely prescribed drug to treat type 2 diabetes. It is a biguanide derivative reducing blood glucose by its capability to regulate energy metabolism, including inhibition of hepatic gluconeogenesis, reduction of glucose absorption, and elevation of glucose utilization in peripheral tissues. In addition, metformin was reported to have cancer prevention. Use of metformin has been associated with a 31% decrease in overall cancer risk, compared with other antidiabetic medications. The capacity of tumor cells for inducing metastasis is a vital feature of their malignant potential, and this capacity may be linked to interactions between tumor cells and platelets. Therefore, tumor cell-induced platelet aggregation (TCIPA) seems to play an important role in tumor metastasis. In the present study, we found that metformin significantly diminished platelet aggregation stimulated by either human hepatoma cells or other endogenous agonists (i.e., collagen). Metformin also significantly suppressed the ATP-release reaction, $[Ca^{2+}]i$ mobilization, and P-selectin expression as well as phospholipase C (PLC)γ2/protein kinase C (PKC), mitogen-activated protein kinase, and phosphoinositide 3-kinase (PI3K)/Akt/glycogen synthase kinase-3 (GSK3) phosphorylation, but no effect in vasodilator-stimulated phosphoprotein phosphorylation in activated human platelets. In animal studies, metformin (250 mg/kg; i.p.) obviously reduced the mortality (from 100% to 50%) associated with acute pulmonary thromboembolism without increasing the bleeding time. Our findings suggest that metformin could be a promising lead as a new class of antiplatelet agent that is effective at inhibiting diabetes-associated arterial thrombosis and TCIPA *in vivo*.

Keywords: Metformin; Tumor cell-induced platelet aggregation; Human hepatoma cells; Human platelets; Pulmonary thromboembolism

Poster 5

Cimetidine Attenuate Cisplatin-Induced Ototoxicity and Nephrotoxicity in Zebrafish Model

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Abstract

Cimetidine is a type of antihistamine that blocks the release of stomach acid. It is used to treat stomach or intestinal ulcers. This medication is a potent inhibitor of organic cation transporters. Cisplatin, one of the most widely-used drugs to treat cancers, induced ototoxicity and nephrotoxicity occurs in inner ear hair cells and kidney proximal tubule epithelial cells, respectively. Recent studies in mice reported that organic cation transporters were identified as cellular uptake mechanisms for cisplatin. In this present study, we investigated whether the organic cation transporter inhibitor, cimetidine, attenuates cisplatin-induced ototoxicity and nephrotoxicity in a zebrafish model. We use vital dye, mitotracker and FM 1-43 for in vivo cellular observation of ionocytes and lateral line hair cells in the skin of zebrafish embryos, respectively. Our results showed that cimetidine can protect hair cells and ionocytes from short-term (2 hr) exposure to 0.5 mM Cisplatin. Cimetidine also attenuated the cisplatin caused hair cell and ionocyte damage in 0-4 dpf (days post fertilization) exposure. The ICP-MS results showed that the Pt accumulated in the embryo after 0-4 dpf cisplatin exposure and cause ion imbalance (Na^+, Ca^{2+}). The co-exposure of cimetidine can revise the cisplatin caused ion imbalance in 0-4 dpf cisplatin treatment. We used SEM (scanning electron microscope) to observe the morphology of neuromast hair cells and the results showed that decreased kinocilium and apical membrane were found in cisplatin exposure embryo for 0-4 dpf, and this tendency could be reversed with co-treatment with cimetidine. Our data suggest a role for Cimetidine as a protective agent against cisplatin-induced hair cell and ionocyte damage.

Keywords: Cisplatin; Cimetidine; Hair cell; Ionocyte; Zebrafish

Poster 6

Expression of Cluster Differentiation 109 Could Be a Potential Biomarker of Immune Checkpoint Inhibitor in Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer death in Taiwan as it is hard for early diagnosis and shows a high capacity for metastasis. Immune checkpoint inhibitors (ICIs) are available for first line of treatment of advanced lung cancer patients. Thus, identifying more reliable indicators of immune checkpoint inhibitors could be a benefit for patient response to immunotherapy and therapeutic outcome. Here, we analyzed transcriptome of lung cancer patients from The Cancer Genome Atlas (TCGA) in conjunction with tumor immune infiltration databases, we identified that cluster differentiation (CD)109, a glycosylphosphatidylinositol-anchored protein, was positively correlated with several well-known efficacy indicators of ICIs including programmed death-ligand 1 (PD-L1), Tumor-infiltration lymphocytes (TILs), and tumor burdens. Moreover, immunohistochemistry staining of lung cancer tissues validated a significantly positive association between CD109 with PD-L1 and CD8. Our study reveals the impact of CD109 on immune component of tumor microenvironment and CD109 may be a potential indicator of immune checkpoint inhibitors.

Keywords: Immune checkpoint inhibitors; Tumor-infiltration lymphocytes; Lung cancer; CD109

Poster 7

Effect of Asiatic Acid and Rigosertib on Proliferation, Apoptosis, and Aerobic Glycolysis in T315I BCR-ABL CML Cells

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Abstract

Chronic myelocytic leukemia (CML) is a myeloproliferative disorder caused by the Bcr-Abl fusion gene, in which the T315I mutation makes CML cells resistant to imatinib. Although the third-generation tyrosine kinase inhibitor ponatinib can inhibit Bcr-Abl kinase, it also has serious side effects. Warburg effect, known as aerobic glycolysis, is an important source of energy acquisition for tumor cells. Previous studies showed that inhibition of Warburg effect may be a promising strategy for cancer therapy. The aim of this study was to explore the influence and mechanism of rigosertib and asiatic acid (AA) on Warburg effect in CML cells with T315I mutation. Rigosertib is a non-ATP competitive multi-targeting inhibitor. It can inhibit CML cell proliferation. AA is a natural small-molecule drug that can induce apoptosis in solid tumor cells. We first found that AA inhibited the proliferation and induced apoptosis in K562, BaF3/p210, and BaF3/T315I cells after 48h treatment. HK1, HK2, HIF1α, PDK1, Glut1, PKM2 and LDHA are the Warburg effect related genes. Rigosertib and AA were able to down regulate HK1, HK2, HIF1α, PDK1, and Glut1 mRNA expression after 48h treatment. Rigosertib and AA have the ability to induce apoptosis in K562, BaF3/p210, and BaF3/T315I cells. These results suggested that rigosertib and AA could induce growth inhibition and apoptosis by inhibiting Warburg effect in CML cells with T315I mutation.

Keywords: Chronic myeloid leukemia; Bcr-Abl T315I resistance; Asiatic acid; Rigosertib

Poster 8

The Development of Quantitative Video-Based Gait Pattern Analysis for Functional Evaluation in the Foot Drop Rat Model Undiced by Ventral Root Avulsion

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Abstract

Foot drop is a gait *impairment* characterized by the inability to raise the foot due to the weakness of dorsiflexors of the foot. Specifically, lumbar spine disorders (e.g., lumbar degenerative disease, intervertebral disc herniation and spinal stenosis) are common neurogenic causes of foot drop. Several studies have been reporting the mechanisms, prognosis factors and surgical treatments of foot drop led by lumbar spine disorders. However, there are a number of controversies. For translational purpose, the use of disease animal models could be the best way to study the pathogenesis and help explore an effective therapeutic strategy for foot drop. Ventral root avulsion in rats has been used as a model for lumbar root injury. Yet, the relationship between gait impairment and the level of ventral root avulsion in such a foot drop animal model has not been determined.

The present study investigated the longitudinal changes of rat's spatiotemporal gait patterns using a video-based walkway platform to acquire footprints and lateral limb images over 21 days period following L5, L6 and L5+L6 ventral root avulsion (VRA) respectively in rats. Our results indicated that L5+L6 VRA rats exhibited changes in gait patterns, including a significantly decreased walking speed, step length, step width, toe spread and duration of swing phase as well as an increased foot angle and duration of stance phase. The ROM also increased at the mid-swing stage, indicating a significant foot drop pattern during locomotion.

We conclude that the proposed foot drop rat model with video-based gait analysis approach can precisely detect the foot drop pattern induced by VRA in rats, which can provide insight into the compensatory changes and recovery in gait patterns and might be useful for serving the translational platform bridging human and animal studies for developing novel therapeutic strategies for foot drop.

Keywords: Foot drop; Ventral root avulsion; Rats

Poster 9

Epigenetic Modulation of Histone Demethylase LSD1 Harnesses Oxidative Stress-Mediated Cell Death in MPNST Cancer Cells

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Abstract

Malignant peripheral nerve sheath tumor (MPNST) is a life-threatening sarcoma. Clinically, MPNSTs are generally refractory to chemo and targeted therapies, and to date there is no FDA approved medication. An increasing body of evidence has shown that the epigenome could be a promising target for cancer therapy. We thus investigated epigenetic factors overexpressed in MPNST and report our study on lysine specific demethylase 1 (LSD1) here. In this study, we examined the hypothesis that LSD1 is expressed in MPNST cancer cells and modulation of LSD1 activity can hamper MPNST growth. Our results showed that LSD1 is overexpressed in MPNST cells. Depletion of LSD1 by siRNA in MPNST cells induces cell apoptosis and arrests cell cycle, resulting in an overall reduced cell viability. Furthermore, LSD1 knockdown followed by RNA-sequencing revealed the induction of TXNIP, a key regulator of oxidative stress by inducing ROS levels. In addition, we found that the new LSD1 inhibitor SP-2577, which blocks both the scaffold domain and the enzymatic domain of the LSD1, is a potent small molecular inhibitor against MPNST. SP-2577-treated MPNST cells showed IC50 values less than 5μM, this activity is associated with significantly increased apoptotic death and cell cycle arrest at G1 phase. SP-2577 treatment also induces TXNIP and ROS levels in time- and dose-dependent manners, confirming the critical of LSD1 in the regulation of ROS homeostasis. Genetic or pharmacological inhibition of LSD1 increases pan-histone H3 methylations on H3K4, H3K9, H3K27, H3K36, and H3K79 sites, these epigenetic switches likely activate TXNIP gene expression, leading to the overwhelmed oxidative stress to MPNST cells. In summary, our study reveals that LSD1 is a promising target for MPNST therapy and LSD1 inhibitor SP-2577 is a potent anti-cancer molecule to induce MPNST lethality.

Keywords: Malignant peripheral nerve sheath tumor (MPNST); Lysine-specific histone demethylase 1 (LSD1); Thioredoxin-interacting protein (TXNIP); Histone H3 methylation

Poster 10

Effects of Air Pollution on Emphysema of Chronic Obstructive Pulmonary Disease: the Role of Hippo Signaling Pathway

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Abstract

We investigated the roles of Hippo signaling pathway components in the emphysema development of rats exposed to traffic-related air pollution. Male 1.5-year-old Fischer 344 ageing rats were exposed to low-level traffic-related air pollution via whole-body exposure system for 3 months with/without high-efficiency particulate air (HEPA) filtration (gaseous vs. particulate matter with aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$)). Lung functions and alveolar destruction (by mean linear intercept) were examined. Western blots and immunofluorescence were used to investigate the signaling pathways associated with Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), cell adherens junctions, differentiation, and senescence. The rats were exposed to 8.7 μg/m^3 $PM_{2.5}$, 10.1 ppb NO_2, 1.6 ppb SO_2, and 23.9 ppb O_3 during the study period. Air pollution exposure decreased forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume in 20 ms (FEV_{20}), and FEF at 25%~75% of FVC (FEF_{25-75}), which coincided with the occurrence of alveolar enlargement. In the lungs of rats exposed to air pollution, we observed increased YAP, phosphorylated (p)-YAP, and pYAP/YAP ratio and increased TAZ, p-TAZ expression, but decreased pTAZ/TAZ ratio. Immunofluorescence staining, however, showed that air pollution exposure decreased pYAP/YAP expression ratio with increasing pTAZ/TAZ ratio in specific surfactant protein-c $(SPC)^+$ alveolar type II cells (AECII). The E-cadherin and α-catenin adherens junction protein were downregulated, whereas the AECII LGALS3 differentiation protein and alveolar type I cells (AECI) protein expression, T1α, were upregulated in rats exposed to traffic-related air pollution. Air pollution exposure also decreased the senescence regulator p-SIRT1/SIRT1 protein ratio in the lung. Our results revealed that air pollution exposure caused emphysema and activated the Hippo signaling pathway, decreasing AECII phosphorylation of YAP and cell adherens junction while increasing AECII phosphorylation of TAZ, AECII-AECI differentiation, and cell senescence.

Keywords: Air pollution; Alveolar enlargement; Lung function; $PM_{2.5}$; YAP/TAZ

Poster 11

Improving Tirapazamine (TPZ) to Target and Eradicate Hypoxia Tumors by Gold Nanoparticle Carriers

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Abstract

Tumor hypoxia plays crucial role in solid tumors and emerged as the therapeutic target for cancer treatments, such as a prodrug Tirapazamine (TPZ) activated in during hypoxia. To increase tumor accumulation, gold nanoparticles (GNPs) were selected to conjugate with TPZ. In this study, we successfully formulated and assessed the biochemical and therapeutic roles of the conjugated GNPs–TPZ combination on therapeutic assessments of MKN45-induced xenograft animal model. The study results indicated that GNPs–TPZ has potential to selectively target hypoxia tumors coupled with decreased side effects on healthy tissue or organs. TPZ significantly reduced cell viability of hypoxic gastric cancer MKN45 cells, but not in cells incubated in normoxia condition. For improving tumor targeting efficiency, furthermore, the GNPs drug carrier was conjugated to TPZ via biding mediator bovine serum albumin (BSA), and we demonstrated that this conjugated GNPs–TPZ retained the unique characteristics of hypoxic toxin and possessed the adequate feature of systemic bio-distributions in animals. GNPs–TPZ nanoparticles revealed their superior affinity to hypoxia tumors in the MKN45 xenograft. Moreover, GNPs–TPZ treatments did not significantly alter the biochemical parameters of blood samples acquired from animals.

Taken together, TPZ, a prodrug activated by hypoxia, was conjugated with GNPs, whereas BSA severed as an excellent binding agent for preparing the conjugated GNPs–TPZ nanomedicines. Our study demonstrated that GNPs–TPZ enhanced tumor targeting, resulting in higher therapeutic efficacy compared to TPZ alone. We suggest that it may sever as an adjuvant treatment or combined therapy with other chemotherapeutics for the treatment of cancer patients in the future.

Keywords: Tumor hypoxia; Drug delivery; Gold nanoparticle; Tirapazamine; Nanomedicine

Poster 12

Combined Impacts of Histamine Receptor H1 Gene Polymorphisms and an Environmental Carcinogen on the Susceptibility to and Progression of Oral Squamous Cell Carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC) is the most frequently encountered type of oral cancer.Histamine receptor H1 (*HRH1*) was reported to play a crucial role in OSCC carcinogenesis, but impacts of genetic variants of *HRH1* on OSCC remain unclear. Herein, we investigated the association between functional single-nucleotide polymorphisms (SNPs) of *HRH1* and OSCC susceptibility or clinicopathologic variables by logistic regression models. *HRH1* genotypes at four loci (rs346074, rs346076, rs901865, and rs2606731) were analyzed by a TaqMan allelic discrimination assay, and we found that patients harboring *HRH1* rs901865 T and rs346074 T alleles had a significantly lower risk of developing larger tumor sizes (>T2) under a dominant model. We observed that *HRH1* rs901865 polymorphic variants were also associated with a lower risk of developing advanced clinical stages (III or IV) in patients with a betel-quid-chewing habit. Moreover, genotype screening of rs901865 and rs346074 in OSCC cell lines showed that cells respectively carrying the CT and TT genotypes expressed lower HRH1 levels compared to cells carrying the CC genotype of rs901865 and rs346074. Furthermore, analyses of TCGA and GEO databases revealed that *HRH1* expression levels were upregulated in OSCC tissues compared to normal tissues and were correlated with larger tumor sizes and poorer prognoses. These results indicated the involvement of *HRH1* SNPs rs901865 and rs346074 in OSCC development and support the interaction between *HRH1* gene polymorphisms and an environmental carcinogen as a predisposing factor for OSCC progression.

Keywords: Oral squamous cell carcinoma; Histamine H1 receptor; Single-nucleotide polymorphisms; Susceptibility; Progression

Poster 13

t-Darpp Exhibits the Role of Tumor Progression in HER2+ Breast Cancer Cells

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Abstract

According to the World Health Organization, breast cancer will surpass lung cancer in the number of new cases in 2020, becoming the first common cancer in the world, which is important to improve the treatment effect of breast cancer. Trastuzumab is one of the important targeted therapy in the clinical treatment of HER2+ breast cancer patients. This antibody can specifically target HER2 on the membrane of cancer cells, thereby reducing the activation of HER2 protein to inhibit the anti-apoptosis and proliferation of cancer cells. According to past research, it shows about 70% of HER2+ breast cancer patients don't achieve the expected effect after treatment with Trastuzumab. Furthermore, some studies detect that t-DARPP protein plays an important role in the resistance of HER2+ breast cancer to Trastuzumab, but the correlation between t-DARPP and HER2 is still unknown. In the report, we applied qPCR to examine the association between human breast cancer tissue with clinical features. In addition, RT-PCR, and western blot were used to determine the correlation between t-DARPP and HER2+ breast cancer cells. we found that t-DARPP protein would express in HER2+ breast cancer cells significantly higher than in other types of breast cancer cells. Moreover, when we knock down the t-DARPP protein expression, we detected that BT-474 will be inhibited the ability of proliferation and migration by cell counter and transwell assay, respectively. However, we don't have useful ways to solve the problem of Trastuzumab resistance in the treatment. So, we want to t-DARPP can be a potential target for HER2+ breast cancer treatment in the future.

Keywords: t-Darpp; HER2+ breast cancer; Trastuzumab

Poster 14

Obesity-induced Metabolic Reprogramming Facilitates Breast Cancer Progression via YAP-Mediated Redox Homeostasis

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Abstract

Obesity is a well-known risk factor for breast cancer, showing an association with increased incidence and poor prognosis. Obesity-induced dysregulation of hormones is considered to be the major factor that promotes breast tumorigenesis; however, obesity has been reported to increase the malignance of triple-negative breast cancer (TNBC), which is a hormone-independent breast cancer subtype. Therefore, identifying the underlying mechanisms behind obesity-associated breast cancer is urgently needed. Here, we found that diet-induced obesity (DIO) enhanced tumorigenesis and metastasis of TNBC cells. Importantly, DIO-induced metabolic reprogramming enables TNBC cells to rely on fatty acid oxidation (FAO) and is accompanied by the activation of Yes-associated protein (YAP) signaling. YAP alleviates FAO-induced metabolic oxidative stress through transcriptional upregulation of antioxidant-related enzymes including glutamate-cysteine ligase catalytic subunit (GCLC), glutathione disulfide reductase (GSR), peroxiredoxin 1 (PRDX1), and methionine sulfoxide reductase A (MSRA), thereby rendering tumor cells survive. Adipocytes-derived fatty acids are identified to be responsible for enhancing the FAO-YAP axis and antioxidative capacity. Furthermore, clinical analyses showed that obesity signature in breast cancer patients is positively correlated with the activation of YAP signaling and the expression of antioxidant genes (*GCLC*, *GSR*, *PRDX1* and *MSRA*). Our findings uncover the crucial role of YAP in dictating mitochondrial redox homeostasis for obesity-mediated metabolic reprogramming and breast tumor progression.

Keywords: Obesity; Breast cancer; Fatty acid oxidation (FAO); Yes-associated protein (YAP)

Poster 15

Human Umbilical-Derived Mesenchymal Stem Cells Facilitate Alveolar Type II Cell Differentiation by YAP Regulation in Acute Respiratory Distress Syndrome (ARDS)

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Abstract

Background: Acute respiratory distress syndrome (ARDS) has shown a poor prognosis in the failure differentiation of alveolar type II (AT2) cells into alveolar type I (AT1) cells by yes-associated protein (YAP). However, the effect of the human umbilical-derived mesenchymal stem cells (hUC-MSCs) on YAP regulation in ARDS remains unclear. Therefore, the objective of this study is to investigate the role of hUC-MSCs in alveolar cell differentiation by regulating YAP in ARDS. The hypothesis is that the reduction of YAP in AT2 cells by hUC-MSCs promotes cell differentiation into AT1 cells in ARDS.

Material and Methods: The male C57BL/6 mice intratracheally received lipopolysaccharide (LPS) to induce ARDS followed by a single dose of hUC-MSC administration from tail veins. The chest computerized tomography (CT) of mice was conducted on day 7. The bronchoalveolar lavage fluid, serum, and lung tissues of mice were collected on days 3 and 7 after euthanasia. In addition, the hUC-MSCs were cocultured with MLE-12 (AT2) cells after treating 0.1 or 1 μg/mL of LPS. The collection of MLE-12 cell lysates was conducted at 6 and 12 hours.

Results: Our results show a decrease in lung injury score and an increase in the alveolar aeration in mice by hUC-MSCs on day 7 after LPS-induced ARDS. We observed the YAP was increased on day 3 and reduced on day 7 by hUC-MSCs in mice lung tissues. Decreased surfactant protein C (SPC), an AT2 cell marker, and increased an AT1 cell marker (T1α) by hUC-MSCs were observed *in vivo* and *in vitro*.

Conclusion: The hUC-MSCs promote AT2 cell differentiation by decreasing YAP in the lungs after LPS-induced ARDS. We find the new aspects of hUC-MSCs in regulating the AT2 cell differentiation by YAP in ARDS.

Keywords: Cell differentiation; Epithelium; Lung; Stem cells

Poster 16

Role and molecular mechanisms of monoamine oxidases B in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is the common of urological cancer and sparse clinical biomarkers are available for predicting the progression of this disease till now. Monoamine oxidases (MAOs) including MAOA and MAOB are enzymes located on the outer membranes of mitochondria, which are responsible for catalyzing degradation of different monoamines. Recently, MAOA has been reported as an oncogenic role in various cancers including RCC, but studies on MAOB have focused mostly on its role in the development of neurodegenerative diseases. **Results:** Clinical databases showed that a higher MAOB expression correlated with the favorable survival, early stage, and small tumor size of patients with clear cell RCC (ccRCC). Moreover, according to the univariate and multivariate analyses, we found that MAOB could be an independent prognostic factor for overall survival in ccRCC patients. In contrast, MAOB did not exhibit clinical significance in patients with papillary RCC (pRCC). In vitro studies found that higher expression of MAOB in primary ccRCC cells (786-O and A498) compared to metastatic ccRCC cells (Caki-1), but pRCC cells (Caki-2 and ACHN) all expressed very low level of MAOB. MAOB overexpression suppressed proliferative, colony forming, and migratory abilities of ccRCC cell lines, whereas MAOB depletion caused by shRNA promoted colony formation and migration of ccRCC cells. Mechanistic investigations found that MAOB overexpression in ccRCC cells can induce S-phase cell cycle arrest and further trigger apoptotic cell death of cells. **Conclusion:** Taken together, the results of our study may provide insights into the application of MAOB as a novel predictor of clinical outcomes and indicate that increasing MAOB expression may be a new approach that can be used for ccRCC treatment.

Keywords:

MAOB, Monoamine oxidases (MAOs), clear cell RCC

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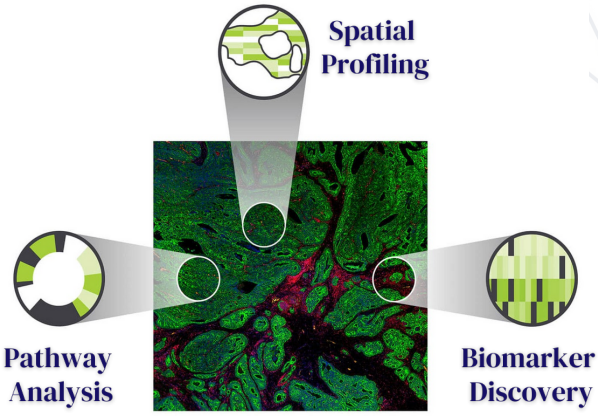

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