2025 Biomedical Research Symposium of National Health Research Institutes

114 年度國家衛生研究院生物醫學學術研討會

Program Book

July 30 - 31, 2025

※ 本摘要集內容請勿擅自引用 ※

National Health Research Institutes, Taiwan

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PRORGAM AT A GLANCE

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09:30	09:30-10:00 **Registration**				09:30
10:00	10:00-10:10 **Opening Remarks** (Venue : Auditorium)			09:50-10:00 Coffee Break	10:00
10:30	10:10-11:00 **Plenary Lecture** (Venue : Auditorium)			10:00-11:00 **Poster Session 2 even numbers**	10:30
11:00	11:00-11:20 Coffee Break				11:00
11:30	11:20-13:00 **Symposium Session 1** : Biomedical Science 1 (Venue : Auditorium)	11:20-13:00 **Symposium Session 2** : Medical Engineering (Venue : Conference Room 2)		11:00-12:40 **Symposium Session 5** Biomedical Science 2 (Venue : Auditorium)	11:00-12:40 **Symposium Session 6** Neuroscience (Venue : Conference Room 2)	11:30
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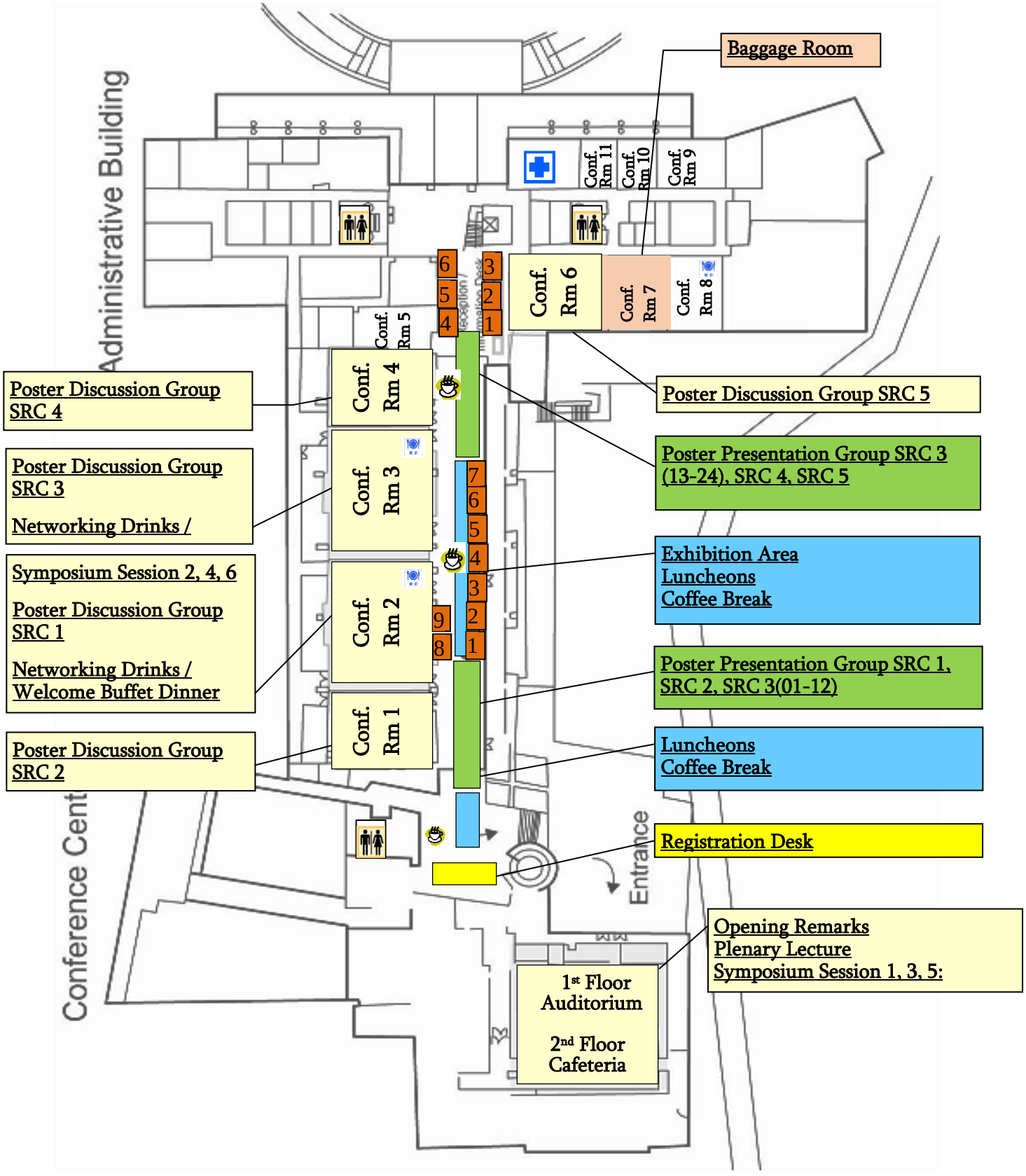
114 年度國家衛生研究院生物醫學學術研討會
2025 Biomedical Research Symposium of National Health Research Institutes
會場分佈圖 (Floor Plan)



用餐區　午餐取餐區/Coffee Break　行李區　茶水區

報到處　壁報張貼區　參展區/ Exhibition Area　研討會會場/Poster Discussion 各分組會場

Daily Program

July 30（Wednesday）

09:30-10:00	**Registration**	
10:00-10:10	**Opening Remarks (Venue : Auditorium)** *Dr. Huey-Kang Sytwu* 司徒惠康院長 National Health Research Institutes 國家衛生研究院	
10:10-11:00	**Plenary Lecture (Venue : Auditorium)** Chairperson: *Dr. Kenneth K. Wu* 伍焜玉院士 National Health Research Institutes / Academia Sinica 國家衛生研究院/中央研究院 **From Untreatable to Curable Disease** **The Paradigm Shift for Lung Cancer Treatment Led to Re-visit of Cancer Biology** *Dr. Chih-Hsin Yang* 楊志新院長 National Taiwan University Cancer Center 國立台灣大學醫學院附設醫院癌醫中心分院	
11:00-11:20	**Coffee Break**	
	Symposium Session 1 : Biomedical Science 1 **(Venue : Auditorium)** Chairpersons: *Dr. Edward T.H. Yeh* 葉篤行院士 University of Arkansas for Medical Sciences *Dr. Su Hao Lo* 羅世皓特聘研究員 National Health Research Institutes 國家衛生研究院	**Symposium Session 2 : Medical Engineering** **(Venue : Conference Room 2)** Chairpersons: *Dr. Zong-Ming Li* 李宗明教授 University of Arizona *Dr. Chia-Wen (Kevin) Wu* 吳嘉文特聘研究員 National Health Research Institutes 國家衛生研究院
11:20-11:45	**PD-1 membrane presentation and stability: Mechanisms and therapeutics** *Dr. Yi-Ching Wang* 王憶卿講座教授 National Cheng Kung University 國立成功大學	**3D High/Super-Resolution Imaging for Human Pancreas Analysis in Health and Disease** *Dr. Shiue-Cheng (Tony) Tang* 湯學成教授 National Tsing Hua University 國立清華大學
11:45-12:10	**Targeting Epigenetic Drivers: KDM4 and PHF8 Demethylase Inhibition in Tumors** *Dr. Wen-Ching Wang* 王雯靜特聘教授 National Tsing Hua University 國立清華大學	**Bioengineered Virus-Like Nanoparticles as Versatile Platforms for Cancer Treatment** *Dr. Hung-Wei Yang* 楊閎蔚教授 National Cheng Kung University 國立成功大學

12:10-12:35	**Epigenetic Regulation of Myocardial SERCA2a and Calcium Homeostasis by Long Noncoding RNA lnc-SYNPO** *Dr. Kai-Chien Yang* 楊鎧鍵教授 National Taiwan University 國立臺灣大學	**Advanced Metasurface Optics for Next-Generation Biomedical Technologies** *Dr. Yuan Luo* 駱遠教授 National Taiwan University 國立臺灣大學
12:35-13:00	**Human mesenchymal stromal/stem cell (hMSC) inter- & intra-source heterogeneity: high-resolution characterization to bridge preclinical-clinical outcome gap** *Dr. B Linju Yen* 顏伶汝研究員級主治醫師 National Health Research Institutes 國家衛生研究院	**Application of AI and High Performance Computing for optimization of treatment parameters during radiofrequency ablation of liver tumor** **CV: Please follow the attachment file** *Dr. Maxim Solovchuk* 馬克沁副研究員 National Health Research Institutes 國家衛生研究院
13:00-14:00	**Lunch**	

	Symposium Session 3 : Cancer Research **(Venue : Auditorium)** Chairpersons: *Dr. Tso-Pang Yao* 姚佐邦教授 Duke University *Dr. Tai-Lung Cha* 查岱龍特聘研究員 National Health Research Institutes 國家衛生研究院	**Symposium Session 4 : Clinical and Public Health** **(Venue : Conference Room 2)** Chairpersons: *Dr. Jiu-Chiuan Chen* 陳居泉教授 University of Southern California *Dr. Hung-Yi Chiou* 邱弘毅特聘研究員 National Health Research Institutes 國家衛生研究院	**Poster Discussion (Venue: Conference Room 4)** Chairperson: *Dr. Zong-Ming Li* 李宗明教授 University of Arizona
14:00-14:25	**From MR Imaging Biomarkers to Immunotherapy: A Translational Approach to Targeted Brain Cancer Treatment** *Dr. Cheng-Yu Chen* 陳震宇教授 Taipei Medical University 臺北醫學大學	**Multimodal Characterization of Autism: Integrating Cognitive, Neuroimaging, and Gut–Brain Axis Data** *Dr. Susan Shur-Fen Gau* 高淑芬特聘教授 National Taiwan University 國立臺灣大學	**Group SRC4 - Medical Engineering**

14:25-14:50	**ADAM9 Inhibition Promotes KRAS Degradation in Pancreatic Cancer Treatment** *Dr. Yuh-Pyng Sher* 佘玉萍教授 China Medical University 中國醫藥大學	**Shaping Hepatocellular Carcinoma Risk: From Viral Etiologies to Metabolic Dysfunction and Beyond** *Dr. Mei-Hsuan Lee* 李美璇教授 National Yang Ming Chiao Tung University 國立陽明交通大學
14:50-15:15	**Rewiring Epigenetic and Metabolic Circuits to Enhance Cancer Immunotherapy** *Dr. Hsing-Chen Tsai* 蔡幸真副教授 National Taiwan University 國立臺灣大學	**An Update of Research Progress in Stroke Rehabilitation** *Dr. Keh-chung Lin* 林克忠教授 National Taiwan University 國立臺灣大學
15:15-15:40	**Uncovering Atypical GPCR Pathway Mediates Cell-intrinsic Adaptation and Extrinsic Communication Contributing to Cancer Progression** *Dr. Tai-Lung Cha* 查岱龍特聘研究員 National Health Research Institutes 國家衛生研究院	**A Continuous Learning Journey: from Clinical Trial Design to Infectious Disease Modeling and Public Health Impact** *Dr. Hsiao-Hui Sophie Tsou* 鄒小蕙研究員 National Health Research Institutes 國家衛生研究院
15:40-16:00	**Coffee Break**	
16:00-17:00	**Poster Session 1 - odd numbers**	
17:00-17:30	**Networking Drinks**	
17:30-19:00	**Welcome Buffet Dinner**	

July 31 (Thursday)

09:00-09:50	**Plenary Lecture (Venue : Auditorium)** Chairpersons: *Dr. Huey-Kang Sytwu* 司徒惠康院長 National Health Research Institutes 國家衛生研究院 **Neuroimmune Dysfunction in FTD Spectrum Diseases** *Dr. Eric Jinsheng Huang* 黃金生院士 Washington University School of Medicine / Academia Sinica	
09:50-10:00	**Coffee Break**	
10:00-11:00	**Poster Session 2 - even numbers**	
	Symposium Session 5 : Biomedical Science 2 (Venue : Auditorium) Chairpersons: *Dr. Reen Wu* 吳忍教授 University of California at Davis *Dr. Shie-Liang Hsieh* 謝世良特聘研究員 National Health Research Institutes 國家衛生研究院	**Symposium Session 6 : Neuroscience (Venue : Conference Room 2)** Chairpersons: *Dr. Lina Wei* 魏麗娜教授 University of Minnesota *Dr. Wei J. Chen* 陳為堅特聘研究員 National Health Research Institutes 國家衛生研究院
11:00-11:25	**Pericyte-specific Targeting for Kidney Disease and Complication** *Dr. Shuei-Liong Lin* 林水龍教授 National Taiwan University 國立臺灣大學	**Hippocampal Mossy Cell Circuitry and Function: Anxiogenic or Anxiolytic?** *Dr. Cheng-Chang Lien* 連正章特聘教授 National Yang Ming Chiao Tung University 國立陽明交通大學
11:25-11:50	**Structure/function mechanisms of CFTR modulators** *Dr. Tzyh-Chang Hwang* 黃自強教授 National Yang Ming Chiao Tung University 國立陽明交通大學	**Cerebellar algorithms for motor control: toward Newtonian precision & cross-individual uniformity** *Dr. Ming-Kai Pang* 潘明楷副教授 National Taiwan University 國立臺灣大學
11:50-12:15	**Ubiquitin ligase RBCK1 deficiency unveils mitochondrial pathways linking glycogen metabolism to cardiomyopathy** *Dr. Su-Yi Tsai* 蔡素宜教授 National Taiwan University 國立臺灣大學	**TRPM2 in Thermosensation and Beyond** *Dr. Chun-Hsiang Tan* 譚俊祥副教授 Kaohsiung Medical University 高雄醫學大學

12:15-12:40	**From deep sea to immunity: Coral-derived STING modulators** *Dr. Mingzi Zhang* 張明姿副研究員 National Health Research Institutes 國家衛生研究院	**Assortative mating across psychiatric disorders is consistent and persistent over cultures and generations** *Dr. Shi-Heng Wang* 王世亨副研究員 National Health Research Institutes 國家衛生研究院
12:40-13:40	**Lunch**	
13:40-15:40	**Poster Discussion (Group SRC1-SRC5)** Chairpersons: **Group SRC 1 - Biomedical Science (Venue: Conference Room 2)** *Dr. Edward T.H. Yeh* 葉篤行院士 University of Arkansas for Medical Sciences **Group SRC 2 - Neuroscience (Venue: Conference Room 1)** *Dr. Lina Wei* 魏麗娜教授 University of Minnesota **Group SRC 3 - Cancer Research (Venue: Conference Room 3)** *Dr. Tso-Pang Yao* 姚佐邦教授 Duke University **Group SRC 4 - Medical Engineering (Venue: Conference Room 4)** *Dr. Zong-Ming Li* 李宗明教授 University of Arizona **Group SRC 5 - Clinical and Public Health (Venue: Conference Room 6)** *Dr. Tun-Hou Lee* 李敦厚教授 Harvard TH Chan School of Public Health	

2025 Biomedical Research Symposium of National Health Research Institutes
-Plenary Speakers-

Dr. Chih-Hsin Yang, National Taiwan University Cancer Center

Dr. Eric Jinsheng Huang, Washington University School of Medicine

Chih-Hsin Yang, M.D. Ph.D.
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https://www.ntucc.gov.tw/ntucc/Fpage.action?muid=225&fid=182

Education

1996-2000	Ph.D., Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taiwan
1979-1986	M.D., School of Medicine, College of Medicine, National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2021–Present	Director, Cancer Research Center, College of Medicine, National Taiwan University
2020–Present	Superintendent, National Taiwan University Cancer Center
2020–Present	Staff Physician, Department of Medical Oncology, National Taiwan University Cancer Center
2020–Present	Visiting Physician, Department of Oncology, National Taiwan University Hospital
2012–Present	Professor, The Ph.D. Program for Translational Medicine, College of Medicine, National Taiwan University
2009–Present	Professor, Graduate Institute of Oncology, College of Medicine, National Taiwan University
2008–Present	Professor, Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University
2008–Present	Professor, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University
2015–2021	Director, Graduate Institute of Oncology, College of Medicine, National Taiwan University
2016–2020	Director, Cancer Administration and Coordination Center, National Taiwan University Hospital
2015–2020	Director, Department of Oncology, National Taiwan University Hospital
1995–2020	Attending Physician, Department of Oncology, National Taiwan University Hospital
2013–2016	Director, Department of Medical Research, National Taiwan University Hospital
2009–2015	Director, Cancer Research Center, National Taiwan University College of Medicine
2009–2015	Associate Director, Department of Oncology, National Taiwan University Hospital

2006–2008	Associate Professor, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine
2006–2008	Associate Professor, Graduate Institute of Clinical Pharmacy, National Taiwan University
2004–2006	Clinical Associate Professor, School of Medicine, College of Medicine, National Taiwan University
2004–2006	Associate Professor, School of Medicine and the Graduate Institute of Clinical Pharmacy, National Taiwan University
2000–2004	Clinical Assistant Professor, College of Medicine, National Taiwan University School of Medicine
1999–2000	Clinical Lecturer, School of Medicine, National Taiwan University
1997–1999	Adjunct Clinical Lecturer, College of Medicine, National Taiwan University School of Medicine
1993–1995	Clinical associate physician, Department of Oncology, Medicine Branch, NCI, NIH , Bethesda, MD, USA
1992–1993	Visiting Scientist, Department of Oncology, Medicine Branch, NCI, NIH, Bethesda, MD, USA
1988–1992	Resident, Department of Internal Medicine, National Taiwan University Hospital

Research Interests

Basic and Clinical Oncology, Anticancer Drug Research and Development, Chemical Drug Resistance, Clinical Trials, New Anticancer Drug Development, Lung Cancer Immune Microenvironment

Major Honors and Awards

2022	Paul A. Bunn Scientific Award, International society for the study of Lung Cancer
2025-	The 28th National Chair Professor Award of the Ministry of Education
2022	Outstanding scholar Award, Phi-Tau-Phi Honor Society Taiwan
2021–2024	The 24th National Chair Professor Award of the Ministry of Education
2021–2024	Chair Professor, National Taiwan University
2019–2021	Outstanding Scholar Award, Foundation for The Advancement of Outstanding Scholarship.
2018	The 62nd Ministry of Education Academic Award
2015–2018	Ministry of Science and Technology Outstanding Research Award
2015	The 22nd TECO Award
2012–2015	National Science Council Outstanding Research Award
2012	Kobayashi Cancer Chemotherapy Research Award, Asian society of Oncology
2012	National Taiwan University Hospital Outstanding Research Award
2009	Hsu, Chien-Tien Outstanding Cancer Research Award, Chinese Oncology Society

From Untreatable to Curable Disease
The Paradigm Shift for Lung Cancer Treatment Led to Re-visit of Cancer Biology

James Chih-Hsin Yang
楊志新

National Taiwan University, Taiwan
National Taiwan University Cancer Center, Taiwan

The biological background of cancer may be determined by genomic alterations of somatic cells, leading to disruptive function of the tissues and organ systems. Since mutations of genome is frequently found in human cells, accumulation of gene mutations and immune escape are among many factors that contribute to carcinogenesis. It is now clear that carcinogenesis and a lengthy process that requires multisteps and mutations in the right direction and combinations. Gene mutations, amplifications or transcriptional, translational alterations may contribute to cancer growth and progression. The evidence of tumor convergence and divergence evolution by acquisition of new mutations and dysfunctions can be found by analysis of different metastatic sites from the same patients. Since many gene alterations are found in a single cancer patient's cancer tissue, it is postulated that molecular targeted therapy that aim at controlling one of the proto-oncogenes may only slow down the tumor grow, leaving the other coexisting oncogenes to take over and continue to grow. However, the successful use of tyrosine kinase inhibitor of epidermal factor growth factor receptor in lung cancer completely changed our view. It seems that at least in lung cancer patients harboring EGFR mutations, all cancer cells were very dependent on mutated EGFR, and upon using correct tyrosine kinase inhibitor, massive cancer cell death was found clinically. Similar observations was also found in lung cancer patients with K-ras, B2 raf, HER2 mutations, RET, ALK, ROS1, NRG1, NTRK fusion genes and cMET skipping mutation. Thus targeted therapy against these mutations were very effective for a certain period to control tumor growth. Interestingly, at the time of diagnosis, These mutated genes seems to be mutually exclusively. After long term treatment (or lung cancer cells under extreme pharmacological stress), interestingly, two of the above mutated genes can occur in the same patient. Cancer progression or resistance after successful therapy were found eventually after a period of successful tumor control. The progression can be explained by tumor evolution and acquisition of new mutations of proto-oncogenes. These gene alterations now can be detected by rebiospy or plasma tests and sometimes dual targeted therapy may be helpful. Unfortunately, due to divergence of evolution, multiple resistance mechanism may occur that make further treatment difficult. Lung cancer was thought to be non-immunogenic, due to many unsuccessful attempt of various immunotherapy. However, the discovery of program death-1 on cytotoxic T cells and program death 1 ligand in cancer cells being the inhibitory checkpoint for cancer cells to evade from immune cells attack provided the rationale to develop monoclonal antibodies against PD1/PDL1 to restore T cells activity against tumors. 10-15% of NSCLC patients had good response to PD1 or PDL1 inhibitors. Recently, several studies indicated that combination of checkpoint inhibitors and chemotherapy can improve overall survival of NSCLC patients over chemotherapy alone. The 5 year survival of stage IV NSCLC have improved from 3% to over 10% in the past 15 years. Advances in our knowledge of the tumor cells and micro-environment may further improve patient's survival and quality of life in the future. The application of PD1/PDL1 inhibitors in cancer patients stemmed from in depth basic research of PD1/PDL1 interaction of T cells and cancer. The successful renaissance of immunotherapy in cancer demonstrated the importance of role of "pure" basic research turned out to be a therapeutic breakthrough in cancer treatment. Conversely, the successful use of both targeted therapy and immunotherapy in far advance lung cancer patients gave us insights of how tumor grow and progression and their interaction with surrounding microenvironments. Lung cancer therapy serve as the best model for translational research in cancer investigation.

Eric Jinsheng Huang, M.D. Ph.D.
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Education

1979 – 1986	B.M., Medicine, National Taiwan University College of Medicine, Taiwan
1988 – 1993	Ph.D., Molecular Biology, Weill Cornell Graduate School of Medicine, New York, NY, U.S.A.
1993 – 1995	Residency in Anatomic Pathology, University of California, San Francisco, CA, U.S.A.
1995 – 1997	Fellowship in Neuropathology, University of California, San Francisco, CA, U.S.A.

Research and Professional Positions Held in Chronological Sequencesxc xc

1997 – 2000	Postdoctoral Fellowship, Howard Hughes Medical Institute (HHMI) & University of California, San Francisco, CA, U.S.A.
2000 – 2005	Assistant Professor, Department of Pathology, University of California, San Francisco, CA, U.S.A.
2005 – 2009	Associate Professor, Department of Pathology, University of California, San Francisco, CA, U.S.A.
2009 – 2024	Professor, Department of Pathology, University of California, San Francisco, CA, U.S.A.
2019 – 2024	Vice Chair of Research, Department of Pathology, University of California, San Francisco, CA, U.S.A.
2000 – 2024	Attending Pathologist, San Francisco Veterans Health Care Systems, San Francisco, CA, U.S.A.
2024	Director, Physician Scientist Scholars Program (PSSP), University of California, San Francisco, CA, U.S.A.
2025 – now	Edward Mallinckrodt Professor & Chair, Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, MO, U.S.A.
2025 – now	Pathologist-in-Chief, Barnes-Jewish Hospital, St. Louis, MO, U.S.A.

Research Interests

I am a physician-scientist with a long-standing interest in the fundamental mechanisms that govern neural development and neurodegeneration.

Major Honors and Awards

1990 – 1991	Frank Lappin Horsfall, Jr. Fellowship, Memorial Sloan-Kettering Cancer Center, New York, NY, U.S.A.
1991	Vincent du Vigneaud Award of Excellence, Weill Cornell Graduate School of Medical Sciences, New York, NY, U.S.A.
1997 – 2000	Postdoctoral Research Fellowship for Physicians, Howard Hughes Medical Institute, Chavy Chase, MD, U.S.A.
2000 – 2005	Presidential Early Career Award for Scientists and Engineers (PECASE)(Given by President Bill Clinton in 1999)
2002 – 2007	Independent Scientist Award, NINDS/NIH
2009 – 2014	Mid-career Investigator Award in Mouse Pathobiology, NCRR/NIH
2014	Chair, Gordon Research Conference on Molecular & Cellular Neurobiology
2016	The DeArmond Lecture, AANP Annual Meeting
2017	The Stowell Lecture, Department of Pathology, University of California, Davis
2018	Keynote Speaker, 27th International Complement Workshop, Santa Fe, NM
2019	Mentoring Award, UCSF BMS Graduate Program
2021	Organizer, Keystone Symposium on Neurodegenerative Diseases
2021	Award of Distinction, Weill Cornell Graduate School of Medical Sciences
2022 – 2023	President, American Association of Neuropathologists (AANP)
2023	Institutional Seminar Speaker, Institute of Biomedical Sciences (IBMS), Academia Sinica
2024	Elected Academician, Academia Sinica, Taipei, Taiwan
2025	Elected Member, Association of American Physicians (AAP)

Neuroimmune Dysfunction in FTD Spectrum Diseases

Eric J. Huang
黃金生

Department of Pathology & Immunology, Washington University School of Medicine, U.S.A.

Mutations in *Progranulin* (*GRN*) and *C9orf72* are common causes of frontotemporal dementia (FTD). In case-control studies, *GRN* or *C9orf72* mutation carriers show a higher propensity to develop autoimmune diseases, whereas *GRN* and *C9orf72* dual mutation carriers manifest early disease-onset and severe autoimmune dysfunction. While these findings suggest that the immune defects in FTD might contribute to neurodegeneration, how *GRN* and *C9orf72* regulate the intersection of adaptive immunity and brain's innate immunity remains unclear. Here we used single-cell transcriptomics to systematically interrogate the autoimmunity and neuroinflammation phenotypes in $Grn^{-/-};C9orf72^{-/-}$ mice. This approach revealed that concurrent loss of *Grn* and *C9orf72* activated pattern recognition receptor TLR7 via phagosome and endolysosomal pathways, which resulted in clonal expansion of age-associated and activated B cells. Consistent with these results, TLR7 agonist Resiquimod elicited a robust expansion of activated $Grn^{-/-};C9orf72^{-/-}$ B cells with increased secretion of proinflammatory cytokines. The same treatment increased FcR-mediated phagocytosis in $Grn^{-/-};C9orf72^{-/-}$ microglia and astrocytes. In addition, the clonally expanded $Grn^{-/-};C9orf72^{-/-}$ B cells produced anti-Robo3 autoantibodies that promoted survival of $Grn^{-/-};C9orf72^{-/-}$astrocytes. Furthermore, cerebrospinal fluids from *GRN* or *C9orf72* mutation carriers showed elevated anti-ROBO3 titers that correlated with disease progression and proinflammatory markers C1q and C3b. Together, these results reveal a synergistic role for *GRN* and *C9orf72* to regulate TLR7 signaling. Concurrent loss of *GRN* and *C9orf72* in regulating TLR7-mediated B cell expansion, autoantibody production, and neuroinflammation in FTD.

2025 Biomedical Research Symposium of National Health Research Institutes
-Invited Speakers-

Session 1: Biomedical Science 1

Dr. Yi-Ching Wang, National Cheng Kung University
Dr. Wen-Ching Wang, National Tsing Hua University
Dr. Kai-Chien Yang, National Taiwan University
Dr. B Linju Yen, National Health Research Institutes

Session 2: Medical Engineering

Dr. Shiue-Cheng (Tony) Tang, National Tsing Hua University
Dr. Hung-Wei Yang, National Cheng Kung University
Dr. Yuan Luo, National Taiwan University
Dr. Maxim Solovchuk, National Health Research Institutes

Session 3: Cancer Research

Dr. Cheng-Yu Chen, Taipei Medical University
Dr. Yuh-Pyng Sher, China Medical University
Dr. Hsing-Chen Tsai, National Taiwan University
Dr. Tai-Lung Cha, National Health Research Institutes

Session 4: Clinical and Public Health

Dr. Susan Shur-Fen Gau, National Taiwan University
Dr. Mei-Hsuan Lee, National Yang Ming Chiao Tung University
Dr. Keh-chung Lin, National Taiwan University
Dr. Hsiao-Hui Sophie Tsou, National Health Research Institutes

Session 5: Biomedical Science 2

Dr. Shuei-Liong Lin, National Taiwan University
Dr. Tzyh-Chang Hwang, National Yang Ming Chiao Tung University
Dr. Su-Yi Tsai, National Taiwan University
Dr. Mingzi Zhang, National Health Research Institutes

Session 6: Neuroscience

Dr. Cheng-Chang Lien, National Yang Ming Chiao Tung University
Dr. Ming-Kai Pang, National Taiwan University
Dr. Chun-Hsiang Tan, Kaohsiung Medical University
Dr. Shi-Heng Wang, National Health Research Institutes

Yi-Ching Wang, Ph.D.
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Education

1983-1987	B.S., Chinese Culture University, Taiwan
1988-1993	Ph.D., Michigan State University, USA

Research and Professional Positions Held in Chronological Sequence

1993-1995	Post-doctoral fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan
1995-1999	Associate Professor, Institute of Toxicology, Chung Shan Medical University, Taiwan
1999-2006	Professor, Department of Life Science, National Taiwan Normal University, Taiwan
2006-2015	Distinguished Professor, Department of Pharmacology & Institute of Basic Medical Science, National Cheng Kung University, Tainan, Taiwan
2015-present	Chair Professor, Department of Pharmacology & Institute of Basic Medical Science, National Cheng Kung University, Tainan, Taiwan
2023-present	Director, Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Research Interests

Dr. Yi-Ching Wang has a long-standing research interest in the molecular mechanisms underlying tumorigenesis, with a primary focus on lung cancer. More recently, her team has expanded their studies to include esophageal carcinoma, pancreatic cancer, and colorectal cancer-among the leading causes of cancer-related deaths worldwide. Her research investigates the etiological roles of tumor suppressor gene and oncogene alterations in cancer signaling pathways, leveraging cancer genomics and epigenomics to identify novel genes critical to tumor development. In recent years, Dr. Wang has directed increasing attention to the study of post-translational modifications of immune inhibitory receptors on T cells, as well as the functional role of Rab37, a small GTPase, in regulating exocytosis and its dysregulation in tumorigenesis and the tumor microenvironment. Her team is actively engaged in the development of novel anti-cancer therapeutics and immunomodulatory antibodies. As a Principal Investigator for the past three decades, Dr. Wang has published 143 SCI-indexed papers (i10-index: 125) in high-impact journals including *Journal of Clinical Investigation*, *Nature Communications*, *Nucleic Acids Research*, *Journal of Thoracic Oncology*, *Cell Death & Differentiation*, *Cancer Research*, *Science Advances*, and *Theranostics*. She has an H-index of 50. In addition, her group has presented 398 conference papers, authored 4 book chapters, and secured 5 Taiwan patents, 3 US patents, and 1 PCT patent, with one technology transferred.

Major Honors and Awards

2024	NSTC Appointed Outstanding Research Award
2023	Tien Te Lee Biomedical Foundation for Excellent Biomedical Award
2022	The Ministry of Education's 66th Annual Academic Award
2021	The Foundation for the Advancement of Outstanding Scholarship Award
2018	K. T. Li Honorary Scholar Award
2017	Dr. Wang Min-Ning Memory Foundation for Excellent Basic Medical Research award
2004,2010,2014	Outstanding Research Award of NSC / MOST
2013	Dr. Tung Ta-Cheng Memorial Award for Basic Cancer Research, Chinese Oncology Society
2011	Outstanding research paper award of National Cheng Kung University
2008-2024	Outstanding research paper award of Cheng Hsin Foundation, Taiwan
2008	Research Award of the Pharmacology Society, Taiwan
2007	Distinguished alumnus of Chinese Culture University, Taiwan

Selected Publications in Five Years

1. Hsieh HC, Young MJ, Chen KY, Su WC, Lin CC, Yen YT, Hung JJ*****, **Yi-Ching Wang***. **2025**. Inhibition of USP24 augments T-cell anti-tumor immunity by destabilizing PD-1. ***Science Advances*** 11(16):eadt4258.
2. WT Kuo, IY Kuo, HC Hsieh, ST Wu, WC Su, **Yi-Ching Wang***. **2024**. Rab37 mediates trafficking and membrane presentation of PD-1 to sustain T cell exhaustion in lung cancer**.** ***J Biomed Sci.*** 7;31(1):20.
3. Hsieh CH, Ho PS, Wang WL, Shih FH, Hong CT, Wang PW, Shieh DB, Chang WL, **Yi-Ching Wang***. **2024**. Decreased plasma gelsolin fosters a fibrotic tumor microenvironment and promotes chemoradiotherapy resistance in esophageal squamous cell carcinoma. ***J Biomed Sci.*** 31(1):90.
4. PS Yang, MH Yu, YC Hou, CP Chang, SC Lin, IY Kuo, PC Su, HC Cheng, WC Su, YS Shan*, **Yi-Ching Wang***. **2022**. Targeting protumor factor chitinase-3-like-1 secreted by Rab37 vesicles for cancer immunotherapy. ***Theranostics,*** 12(1):340-361. **(cover article)**
5. CH Hsieh, WH Kuan, WL Chang, IY Kuo, H Liu, DB Shieh, H Liu, B Tan, **Yi-Ching Wang***. **2022**. Dysregulation of SOX17/NRF2 axis confers chemoradiotherapy resistance and emerges as a novel therapeutic target in esophageal squamous cell carcinoma. ***J Biomed Sci.*** 29(1):90.
6. IY Kuo, YE Yang, PS Yang, YJ Tsai, HT Tzeng, HC Cheng, WT Kuo, WC Su, CP Chang*, **Yi-Ching Wang***. **2021.** Converged Rab37/IL-6 trafficking and STAT3/PD-1 transcription axes elicit an immunosuppressive lung tumor microenvironment. ***Theranostics*** 11(14):7029-7044. **(cover article)**
7. CH Hsieh, HC Hsieh, FH Fu, PW Wang, LX Yang, DB Shieh*, **Yi-Ching Wang*. 2021**. An innovative NRF2 nano-modulator induces lung cancer ferroptosis and elicits an immunostimulatory tumor microenvironment. ***Theranostics,*** 11(14):7072-7091. **(cover article)**

PD-1 Membrane Presentation and Stability: Mechanisms and Therapeutics

Yi-Ching Wang
王憶卿

Department of Pharmacology, Institute of Basic Medical Sciences,
College of Medicine, National Cheng Kung University, Taiwan

Immune checkpoint regulation plays a pivotal role in cancer immune evasion. Our recent studies uncover two critical post-translational mechanisms that sustain T cell exhaustion in the lung tumor microenvironment (TME) through the modulation of PD-1. First, we identified the small GTPase Rab37 as a vesicular trafficking mediator that dynamically regulates PD-1 plasma membrane presentation in a GTP- and glycosylation-dependent manner. Elevated Rab37 expression in CD8+ T cells correlates with increased PD-1/TIM3 co-expression and poor survival in lung cancer patients, highlighting Rab37+/PD-1+/TIM3+ T cells as a novel prognostic biomarker. Second, we demonstrated that USP24, a deubiquitinase transcriptionally induced by IL-6/STAT3/NF-κB signaling, stabilizes PD-1 by removing K48-linked polyubiquitin chains. Genetic ablation or pharmacological inhibition of USP24 enhances CD8+ T cell cytotoxicity and synergizes with anti-CTLA4 therapy to suppress lung tumor growth in vivo. Clinically, high infiltration of USP24+/PD-1+/Lag3+ CD8+ T cells was associated with poor prognosis and immunotherapy resistance. These findings elucidate a coordinated network of PD-1 trafficking and stabilization governed by Rab37 and USP24, underscoring their significance in sustaining T cell exhaustion and immune suppression. Targeting the Rab37/PD-1 vesicle axis and USP24-mediated deubiquitination represents a promising strategy to improve the efficacy of immune checkpoint blockade therapies in lung cancer.

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Education

1979-1983	B.S., Agricultural chemistry, National Taiwan University, Taiwan
1983-1985	M.S., Chemistry, University of California, Santa Barbara, US
1988-1992	Ph.D., Chemistry, California Institute of Technology, US

Research and Professional Positions Held in Chronological Sequence

2014	Visiting Research Scholar, Department of Bioengineering, University of California, San Diego, US
2008-2009	Chair of Bioresource Section (生物處學門召集人), Biology Division, National Since Council, Taiwan, R.O.C.
2006-2006	Visiting scholar, Biology, California Institute of Technology, US
2006-2009	Jointly Appointed Professor, Biological Science and Technology, National Chiao
2015-present	Tung University
1992-1995	Lecturer, Life Science, National Tsing Hua University
1995-2002	Associate Professor, Life Science, National Tsing Hua University
2008-2011	Director, Molecular and Cellular Biology, National Tsing Hua University
2002-present	Professor, Life Science, National Tsing Hua University
2009-2016	Director, Biomedical Science and Engineering Center, National Tsing Hua University
2009-present	Distinguished Professor, Life Science, National Tsing Hua University

Research Interests

1. Cancer metabolism and epigenetic regulation in cancer cells.
2. Structure-based discovery of anti-microbial/anti-cancer agents.
3. Pathogenic and resistance mechanism of *Helicobacter pylori*.

Major Honors and Awards

1998-2000	NSC Excellence Award
2002	Wu Da-Yeu Memorial Award
2001 & 2003	Veterans General Hospital-National Tsing Hua University-National Yang Ming University Best Thesis Award
2003	NSC Outstanding Scholar Award
2007-2008	Research Excellency Professor of National Tsing Hua University
2009-2012	MOST Outstanding Scholar Project
2009-2013	Distinguished Professor of National Tsing Hua University

KDM4 and PHF8: Chromatin Demethylase Vulnerabilities in Tumors

Wen-Ching Wang[1*], Meng-Jen Wu[1], Shan-Min Yang[1], Ding-Jun Huang[1], Lin-Lu Tseng[1], Pei-Lien Chen[1], Chung-Yung Ma[2], Chiou-Hwa Yuh[2], Mei-Ling Cheng[3], Hsing-Jing Kung[4], Muh-Hwa Yang[5]
王雯靜[1], 吳孟臻[1], 楊善閔[1], 黃鼎鈞[1], 曾琳蘆[1], 陳沛蓮[1], 馬崇勇[2], 喻秋華[2], 鄭美玲[3], 龔行健[4], 楊慕華[5]

[1]Institute of Molecular and Cellular Biology and Department of Life Science, National Tsing-Hua University, Taiwan.
[2]Institute of Cellular and System Medicine, National Health Research Institutes, Taiwan.
[3]Department of Biomedical Sciences, College of Medicine, Chang Gung University, Taiwan.
[4]Graduate Institute of Cancer Biology and Drug Discovery, Taipei Medical University, Taiwan.
[5]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taiwan

Aggressive tumors exploit histone demethylases to maintain malignant transcription and metabolism. The KDM4 paralogues drive distinct oncogenic pathways: KDM4B amplifies c-Myc glycolytic programs in castration-resistant prostate cancer (CRPC), and KDM4C partners with GATA1 to enhance heme synthesis in head and neck squamous cell carcinoma (HNSCC). Selective KDM4 inhibitors with sub-micromolar potency have been developed to curb the growth of CRPC and HNSCC. In gastric cancer, PHF8 recruits c-JUN, which upregulates *PRKCA* (encoding PKCα) and *MKRN1*, an E3 ligase that ubiquitinates PTEN, subsequently activating the PKCα–Src signaling axis and promoting invasion. Silencing PHF8 stabilizes PTEN, disrupts mitochondrial homeostasis, and suppresses tumor progression. An AI-guided screen identified a synergistic combination of midostaurin and bosutinib that blocks the PHF8–MKRN1 pathway, impairs migration *in vitro*, and reduces zebrafish xenograft progression, particularly in MKRN1-deficient cells. These findings position KDM4 and PHF8 as actionable epigenetic targets; targeting their catalytic or cofactor interactions presents a promising strategy in precision oncology to exploit shared metabolic vulnerabilities.

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Education

1994-2000	M.D. National Taiwan University, Taipei, Taiwan
2003-2005	M.Sc., Medical Sciences, National Taiwan University, Taipei, Taiwan
2007-2012	Ph.D., Molecular Genetics and Genomics, Division of Biology and Biomedical Sciences, Washington University, St Louis, MO, USA

Research and Professional Positions Held in Chronological Sequence

2000-2003	Residency in Internal Medicine. Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2003-2005	Clinical Fellowship in Cardiology. Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2005-2007	Attending Physician and Lecturer, Division of Cardiology, Department of Internal Medicine, E-Da Hospital, Kaohsiung, Taiwan
2012-2014	Post-Doctoral Research Associate, Samuel Dudley's lab, Section of Cardiology, Department of Medicine, University of Illinois at Chicago/Brown University
2014-2019	Assistant Professor, Graduate Institute of Pharmacology, National Taiwan University, Taipei, Taiwan
2014-	Attending Physician, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2019-2022	Associate Professor, Graduate Institute of Pharmacology, National Taiwan University, Taipei, Taiwan
2020 Aug-	Joint Associate Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
2021 Aug-	Deputy director, Center for Frontier Medicine, National Taiwan University Hospital
2022 Aug-	Professor, Graduate Institute of Pharmacology, National Taiwan University

Research Interests

1. Role of long noncoding RNA in Cardiovascular Diseases
2. Pathogenesis and molecular mechanisms of cardiac and organ fibrosis
3. Cardiac inflammation and regeneration

Major Honors and Awards

2007-2009	Ministry of Education Scholarship for Study Abroad, Taiwan

2009-2011	Predoctoral Fellowship Award, American Heart Association Midwest Affiliation
2012	Council on Basic Cardiovascular Sciences Abstract Travel Award, American Heart Association
2013-2014	Postdoctoral Fellowship Award, American Heart Association Midwest Affiliation
2014	Benjamin N. Chiang Outstanding Young Investigator Award in Cardiovascular Medicine Research
2016	First Prize, Award of Basic Science Paper Competition, Taiwan Society of Cardiology
2017	First Prize, Young Investigator Award of the 47th Annual Convention & Scientific Session of the Taiwan Society of Cardiology
2019	Outstanding Biomedical Research Award by Ching-Shin Foundation Dean Cheng-Yuan Lee Memorial Research Award, NTU School of Medicine Outstanding Research Award for Junior Faculty, NTU Hospital
2021	Outstanding Research Award, Taiwan Ministry of Science and Technology Wu Ho-Su TBF Medical Award
2022	The 18th Tien Te Lee Biomedical Awards
2023	Outstanding Research Award, National Taiwan University Hospital
2024	Elected Fellow of European Society of Cardiology (FESC) International Visiting Professorship Award, American Heart Association Outstanding Investigator Award, Taiwan Society of Lipids & Atherosclerosis Taiwan Bio-development Foundation (TBF) Chair Professor Award
2025	Outstanding Research Award, National Science and Technology Council, Taiwan

Selective Recent Representative Publications

1. YW Tsai et al and **KC Yang***. N-Cadherin Promotes Cardiac Regeneration by Potentiating Promitotic β-Catenin Signaling in Cardiomyocytes. ***Nature Communications*** 2025 Jan 21;16(1):896 (**Corresponding author**).
2. CT Hung, TH Su, YT Chen, YF Wu, YT Chen, SJ Lin, SL Lin, **KC Yang***. Targeting ER Protein TXNDC5 in Hepatic Stellate Cell Mitigates Liver Fibrosis by Repressing Non-Canonical TGFβ Signaling. ***Gut*** 2022 Sep;71(9):1876-1891. (**Corresponding author**)
3. CF Yeh et al and **KC Yang*.** Targeting Mechano-sensitive Endothelial TXNDC5 to Stabilize eNOS and Reduce Atherosclerosis in vivo. ***Science Advances*** 2022 Jan 21; 8(3):eabl8096 (**Co-corresponding author**)
4. YT Chen et al and **KC Yang***. Endoplasmic Reticulum Protein TXNDC5 Promotes Renal Fibrosis by Enforcing TGFβ Signaling in Kidney Fibroblasts. ***Journal of Clinical Investigation*** 2021 (Accepted). (**Corresponding author**)
5. TH Lee et al and **KC Yang***. Fibroblast-enriched Endoplasmic Reticulum Protein TXNDC5 Promotes Pulmonary Fibrosis by Augmenting TGFβ Signaling through TGFBR1 Stabilization. ***Nature Communications*** 2020 Aug 26; 11(1):4254. (**Corresponding author**).
6. YC Shih et al and **KC Yang***. Endoplasmic Reticulum-Resident Protein TXNDC5 Augments Myocardial Fibrosis by Facilitating Extracellular Matrix Protein Folding and Redox-Sensitive Cardiac Fibroblast Activation. ***Circulation Research*** 2018; 122(8):1052-1068 (**Corresponding author**).

Epigenetic Regulation of Myocardial SERCA2a and Calcium Homeostasis by Long Noncoding RNA lnc-SYNPO

Kai-Chien Yang
楊鎧鍵

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Background: Heart failure (HF) is characterized by abnormal sarcolemmal Ca^{2+} handling and impaired contractility, largely due to the downregulation of sarcoendoplasmic reticulum calcium ATPase (SERCA2a). However, no clinically approved therapy directly targets SERCA2a dysregulation. Here, we identify the long noncoding RNA lnc-SYNPO as a novel epigenetic regulator of SERCA2a and a potential therapeutic target for HF.

Results: Lnc-SYNPO, derived from the 3' untranslated region of the SYNPO2b gene, was markedly upregulated in failing mouse and human left ventricles, exhibiting an inverse correlation with SERCA2a expression. Lnc-SYNPO knockdown in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and neonatal mouse cardiomyocytes restored SERCA2a levels, Ca^{2+} homeostasis, and contractility, whereas its overexpression had the opposite effect. Mechanistically, ATAC-seq revealed that lnc-SYNPO depletion increased chromatin accessibility at the SERCA2a promoter. RNA pull-down and CUT&RUN-qPCR demonstrated that lnc-SYNPO directly binds to the SERCA2a promoter and recruits EZH2, a core component of the polycomb repressive complex 2 (PRC2), leading to epigenetic silencing of SERCA2a. Furthermore, lnc-SYNPO was upregulated transcriptionally in cardiomyocytes by endothelin-1 (ET-1), a neurohumoral factor elevated in HF, through activating calcineurin-NFAT1 signaling axis. Calcineurin inhibition blocked ET-1-induced lnc-SYNPO upregulation, and luciferase reporter and EMSA assays confirmed that NFAT1 binds to and activates the lnc-SYNPO promoter. Importantly, inducing cardiomyocyte-specific lnc-Synpo deletion restored Serca2a expression, preserved cardiac contractile function, and prevented left ventricular dilation following ischemia-reperfusion injury in mice.

Conclusion: Our study unveiled a previously undiscovered epigenetic regulatory mechanism of SERCA2a by lnc-SYNPO, contributing to impaired myocardial Ca^{2+} homeostasis and contractile dysfunction observed with HF. Targeting lnc-SYNPO, therefore, could be a novel therapeutic approach to improve Ca2+ homeostasis and contractile function in the human failing heart.

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Education

1986-1991	B.A., *Summa cum Laude*, Music (Double Specialization: History/Literature & Performance), School of Fine Arts, University of California at Los Angeles (UCLA), U.S.A.
1991-1996	M.D., School of Medicine, University of California at San Francisco (UCSF), U.S.A.

Research and Professional Positions Held in Chronological Sequence

1993-1994	Post-Sophomore Fellow, Dept. of Pathology, UCLA
1996-1997	Resident/Post-Graduate Year (PGY) 1, Dept. of Obstetrics/Gynecology (ObGyn), UCLA
1998-2001	Resident/PGY 2, PGY3, & Chief Resident, Dept. of ObGyn, National Taiwan University-En Chu Kong Hospital Joint Program
2002-2005	Postdoctoral Fellow, Stem Cell Research Center, National Health Research Institutes (NHRI), Taiwan
2003/3	Visiting Scientist, Embryonic Stem Cell Research Center, UCSF
2005-2009	Assistant Investigator & Attending Physician, Regenerative Medicine Research Group (RMRG—formerly Stem Cell Research Center), Institute of Cellular and System Medicine (ISCM), NHRI
2009-2014	Associate Investigator & Attending Physician, RMRG, ISCM, NHRI
2017/9-23/8	Deputy Director, ISCM, NHRI *Hiatus: 2019/8~20/7 due to sabbatical leave
2014-present	Investigator & Attending Physician, RMRG, ISCM, NHRI

Research Interests

Human mesenchymal stem/stromal cell (MSC) biology & immunobiology, induced pluripotent stem cell (iPSC) biology, cell therapy, women's health

Major Honors and Awards

1989	Distinguished Scholar Award, UCLA
1991	Induction into Phi Beta Kappa National Honor Society, USA
1991	Outstanding Graduating Senior Award, UCLA
1992	UCSF/University of Heidelberg, Exchange Student Scholarship
1996	UCSF/Peking Union Medical College, Exchange Student Scholarship
1997	Best Resident Award, Department of ObGyn, UCLA
2009	Wu Ta-You Young Scientist Award, National Science Council, Taiwan
2010	Junior Researcher Award, Academia Sinica, Taiwan

2010	Young Researcher Achievement Award, NHRI
2013	10th National Innovation Award—Academic Research Category, Institute for Biotechnology & Medicine Industry (IBMI), Taiwan
2015	Outstanding Research Achievement Award, NHRI

Human Mesenchymal Stromal/Stem Cell (hMSC) Inter- & Intra-source Heterogeneity: High-resolution Characterization to Bridge Preclinical-clinical Outcome Gap

Betty Linju Yen
顏伶汝

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National Health Research Institutes, Taiwan

Substantial pre-clinical accumulation of mechanistic and therapeutic reports has allowed rapid translation of human mesenchymal stromal/stem cells (hMSCs) into clinical trials, with over 1500 currently registered worldwide. These versatile progenitor/stem cells possess multilineage differentiation capacity and profound immunomodulatory properties to allow for unmatched use as off-the-shelf cellular products in a wide range of disease indications. But while the safety profile of hMSC therapy has been excellent, only a handful of trials have shown clinically effectiveness. As with all live-cell products, hMSCs are inherently complex products, but the availability of many tissues/organ sources adds another level of complexity which we and others have demonstrated; moreover, hMSCs are known to be heterogeneous, with non-therapeutic subpopulations possibly dampening overall effectiveness. However, the current criteria used to classify hMSCs is nearly 2 decades old and lacks the molecular resolution to reveal these many levels of complexity. To resolve the current therapeutic bottleneck, we turned to whole transcriptome profiling using the microarray platform to rapidly assess inter-source heterogeneity, and antibody-based single-cell RNA sequencing (AbSeq)—a multi-omic profiling platform—to additionally assess intra-source heterogeneity. Utilizing multiple sources of hMSCs, we found all sources cluster together, distinct from other closely related cell types but still exhibiting inter-source differences. AbSeq further exposed the details of inter- as well as intra-source heterogeneity, as well as revealing a small core subpopulation/cell cluster present across different sources. We also evaluated hMSC transcriptomic shift after interactions with activated human T lymphocytes, a key target cell of hMSC therapy, and surprisingly found formation of new hMSC clusters enriched predominantly for immune-related processes unrelated to baseline clusters. Functional validation and further bioinformatics analyses to assess for possible new criteria formation are ongoing. These findings demonstrate the ability of high-resolution technology to unravel the many layers of hMSC complexity and trajectories of functional states to inform and improve clinical application.

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Education

1988-1994	B.S., & M.S. Chemical Eng., National Cheng Kung University, Taiwan
1998-2003	Ph.D., Chemical & Biomolecular Eng., Georgia Institute of Technology , USA
2004	Postdoctoral Fellow, Pediatric Gastroenterology, Stanford University School of Medicine, USA

Research and Professional Positions Held in Chronological Sequence

2005-2008	Assistant Professor, National Tsing Hua Univ., Taiwan, Dept. of Chemical Eng.
2008-2011	Associate Professor, National Tsing Hua Univ., Taiwan, Dept. of Chemical Eng.
2011-2012	Professor, National Tsing Hua Univ., Taiwan, Dept. of Chemical Eng.
2015	Visiting Scholar, Diabetes Center, UCSF (on sabbatical)
2012-present	Professor, National Tsing Hua Univ., Dept. of Medical Science

Research Interests

High-refractive-index polymer synthesis for tissue clearing
Solid-state tissue clearing for antifade 3D/super-resolution imaging
3D gastrointestinal histology
3D pancreatic and islet imaging in health, obesity and diabetes
Pancreatic early lesion, cancer microenvironment, and type 3c diabetes

Major Honors and Awards

Present	American Gastroenterological Association (AGA) Fellow
2024	Outstanding Research Award, National Science & Technology Council, Taiwan
2014-2020	Five-time winner of Nature Reviews Cover Image Competition www.nature.com/collections/fifigibgci (Endocrinology 2014, 2017 and 2019; Nephrology 2015 and 2020)
2013-2024	Cover images on Diabetologia (2013, 2021); EBioMedicine (2015); AJP-GI (2013); AJP-Endo (2022, 2024)
2011, 2017	Research highlighted by Nature Reviews Gastroenterology & Hepatology, editorial report
2011	Scientific Paper Award, Far Eastern Y. Z. Hsu Science & Technology Memorial Foundation, Taiwan
2011	Academia Sinica Young Investigator Award, Taiwan (on 3D gastrointestinal histology)
2009	National Science Council Young Investigator Award, Taiwan, 2009 (on gene delivery)

3D High/Super-Resolution Imaging for Human Pancreas Analysis in Health and Disease

Shiue-Cheng (Tony) Tang
湯學成

Department of Medical Science/Institute of Biotechnology/Department of Chemical Engineering (joint appointment), National Tsing Hua University, Taiwan

The human pancreas is a metabolically essential organ, coordinating both digestive enzyme secretion and blood glucose regulation through its exocrine and endocrine functions. To understand how these tightly integrated systems become disrupted in diseases such as diabetes and pancreatic cancer, high-resolution 3D imaging of pancreatic architecture—including its neurovascular and neuroendocrine networks—is critically needed. Yet, visualizing human pancreatic tissue at subcellular resolution remains technically challenging due to inherent issues such as tissue opacity, autofluorescence, photobleaching, and specimen variability. In this talk, I will present a 3D high/super-resolution imaging platform designed for human pancreas analysis. This system enables detailed visualization of both exocrine and endocrine compartments—including the ductal network and islets—in healthy donor tissue and in early-stage lesion remodeling.

At the core of this platform is a UV-polymerized, high-refractive-index acrylamide-based copolymer that allows for solid-state, solvent-free embedding of fluorescently labeled specimens. This antifade matrix significantly enhances photostability and optical clarity, supporting repeated high-power 3D fluorescence imaging. The workflow is fully compatible with advanced imaging modalities such as 3D Airyscan, STED, and structured illumination microscopy, providing deep-tissue, subcellular resolution at the level of vesicles and cytokeratins. These capabilities allow for precise visualization and analysis of duct–β-cell clusters within remodeled pancreatic lobules—structures of growing biological and clinical significance.

This presentation will offer practical insights into applying advanced imaging technologies to human tissue research. It will be of particular interest to investigators and engineers working in biomedical imaging, microscopy, metabolic disease, and pancreas-focused studies in health and cancer. By demonstrating how polymer science and high-resolution microscopy can be integrated into a robust and reproducible workflow, this talk highlights the role of engineering-driven innovation in advancing our understanding of pancreatic structure and disease.

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Education

2004-2006	M.S., Department of Chemical and Materials Engineering, Chang Gung University, Taiwan
2006-2011	Ph.D., Department of Chemical and Materials Engineering, Chang Gung University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2011~2013	Postdoctoral Fellow, National Tsing Hua University, Taiwan
2013~2014	NIH Postdoctoral Fellow, Georgia Institute of Technology, USA
2014~2018	Assistant Professor, Institute of Medical Science & Technology, National Sun Yat-sen University, Taiwan
2018~2021	Associate Professor, Institute of Medical Science & Technology, National Sun Yat-sen University, Taiwan
2021~2022	Professor, Institute of Medical Science & Technology, National Sun Yat-sen University, Taiwan
2022~	Professor, Department of Biomedical Engineering, National Cheng Kung University, Taiwan

Research Interests

Biopolymer and hydrogel design

NanoBiomaterials design

Virus-like particles delivery system

Drug, DNA, RNAi, vaccine delivery

Microneedles for intradermal drug/vaccine delivery

Smart biosensing system

Major Honors and Awards

2016	The 13th National Innovation Award, Taiwan
2017	Outstanding Paper Award, Association of Chemical Sensors in Taiwan
2017-2021	Project for Excellent Junior Research Investigators, Ministry of Science and Technology
2018	Excellent Academic Research Award, National Sun Yat-sen University
2019	Outstanding Paper Award, Association of Chemical Sensors in Taiwan

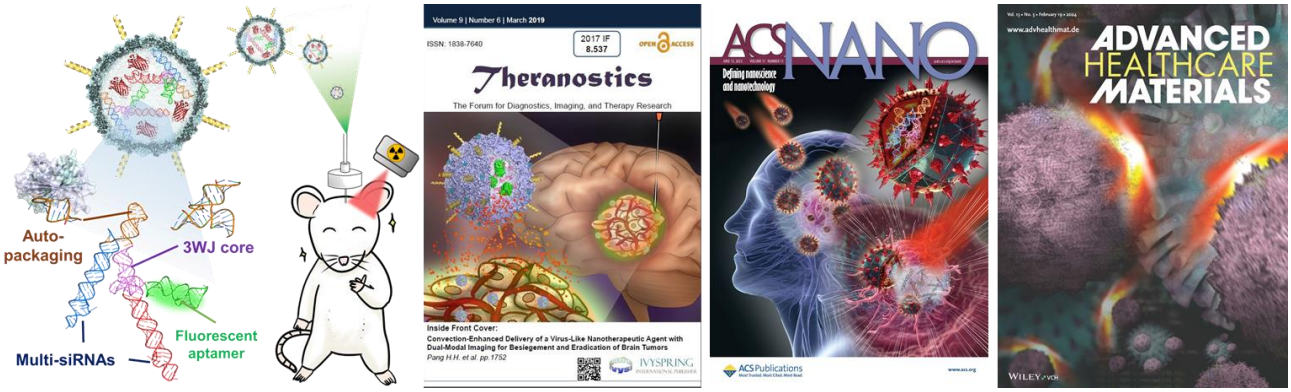
2019	Excellent Academic Research Award, National Sun Yat-sen University, Taiwan
2019-2022	Distinguished Young Scholar Award, National Sun Yat-sen University, Taiwan
2020	Outstanding Paper Award, Association of Chemical Sensors in Taiwan
2021	Outstanding Paper Award, Association of Chemical Sensors in Taiwan
2021	The 18th National Innovation Award, Taiwan
2021	The 2021 Ta-You Wu Memorial Award (Biomedical Engineering)
2022	Outstanding Paper Award, Association of Chemical Sensors in Taiwan
2023	The 2023 Future Tech Award, Taiwan
2023	The 20th National Innovation Award, Taiwan
2024	The 21st National Innovation Award, Taiwan

Bioengineered Virus-Like Nanoparticles as Versatile Platforms for Cancer Treatment

Hung-Wei Yang
楊閎蔚

Department of Biomedical Engineering, National Cheng Kung University, Taiwan

Virus-like nanoparticles (VLNPs) have emerged as powerful nanocarriers for cancer therapy, offering the ability to encapsulate and deliver a wide range of therapeutic cargos with high precision and biocompatibility. In our recent work, we developed a series of bioengineered bacteriophage Qβ-derived VLNPs capable of autonomous *in vivo* packaging of designed RNA scaffolds, including a library of multi-armed RNA motifs (2-WJ, 2.5-WJ, 3-WJ, 4-WJ) for co-delivery of diverse siRNA (i.e., siEGFR, sic-MET, siMGMT, and siNF-κB), miRNA (i.e., Let-7g), and anti-miR (i.e., anti-miR-10b and anti-miR-21) sequences. These RNAi-loaded VLNPs can efficiently cross the blood–brain barrier (BBB), particularly when conjugated with ApoE and cell-penetrating peptides, and have demonstrated significant tumor suppression via gene silencing and synergy with chemotherapy or radiotherapy in glioblastoma models. To further enhance their functionality, we engineered these VLNPs with fusion domains and infused them with gas to form nanobubbles, enabling their use as both ultrasound contrast agents and transient BBB-opening agents. These VLNP-derived nanobubbles (VLNBs) allow real-time ultrasound imaging and spatiotemporally controlled delivery of RNA or drugs into the brain parenchyma. By integrating the diagnostic and therapeutic capabilities into a single platform, our VLNP and VLNB systems represent a versatile and modular toolkit for precision oncology. Our findings underscore the potential of virus-inspired nanotechnology to overcome key challenges in targeted delivery, multi-gene modulation, and image-guided therapy, paving the way for next-generation theranostic strategies for malignant tumors and other diseases.



References:

1. P.Y. Fang, et al. Functional RNAs: Combined assembly and packaging in VLPs. *Nucleic Acids Research* **45**, 3519-3527 (2017).
2. H.H. Pang, et al. Convection-enhanced delivery of a virus-like nanotherapeutic agent with dual-modal imaging for besiegement and eradication of brain tumors. *Theranostics* **9**, 1752-1763 (2019).
3. H.H. Pang, et al. Bioengineering fluorescent virus-like particle/RNAi nanocomplexes act synergistically with temozolomide to eradicate brain tumors. *Nanoscale* **11**, 8102-8109 (2019).
4. H.H. Pang, et al. Bioengineered bacteriophage-like nanoparticles as RNAi therapeutics to enhance radiotherapy against glioblastomas. *ACS Nano* **17**, 10407–10422 (2023).
5. H.H. Pang, et al. AI-driven design system for fabrication of inhalable nanocatchers for virus capture and neutralization. *Advanced Healthcare Materials* **13**, 2302927 (2024).

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Education

2004–2008 **Ph.D., College of Optical Sciences,** University of Arizona, USA
2004–2007 **M.S., College of Optical Sciences,** University of Arizona, USA

Research and Professional Positions Held in Chronological Sequence

2023–present **Director**, Program for Precision Health and Intelligent Medicine, Graduate School of Advanced Technology, National Taiwan University.
2020–present **Director**, Institute of Medical Device and Imaging, College of Medicine, National Taiwan University.
2018–present **Associate Dean**, YongLin Institute of Health, National Taiwan University.
2019–present **Professor**, Institute of Medical Device and Imaging/Department of Biomedical Engineering, National Taiwan University.
2015–2019 **Associate Professor**, Institute of Medical Device and Imaging, National Taiwan University
2014–2015 **Assistant Professor**, Institute of Medical Device and Imaging, National Taiwan University.
2011–2015 **Assistant Professor**, Center for Optoelectronic Biomedicine & Molecular Imaging Center, National Taiwan University.
2009–2011 **Postdoctoral Associate**, 3D Optics Laboratory, Department of Mechanical Engineering, Massachusetts Institute of Technology.
(Transformation optics work was highlighted in Nature News, Dec. 2010, and also selected as the 4th out of the top 10 breakthrough inventions of 2010 in Physics World.)

Research Interests

- Novel optical microscopy and endoscopy
- Optical Holography and Diffractive Optics
- Development and applications of metasurfaces for biological imaging

Fellowship

2024 ***Fellow**, Taiwan Bio-development Foundation Award* (財團法人台灣生技醫藥發展基金會學術講座)
2023 ***Fellow***, SPIE

Major Honors and Awards

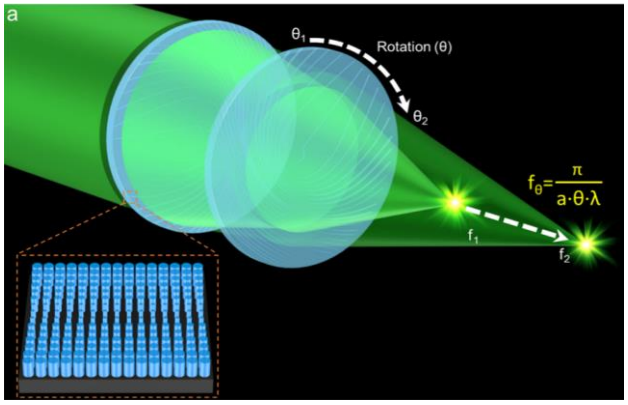
2025	***Nature Photonics Award***, The 11th International Conference on Surface Plasmon Photonics (SPP11)*,* Japan. (supervise two graduates Min-Xuan Wang & YuHsin Chia for poster presentation in SPP11)
2023 – Present	***Review Committee Member***, Division of Optoelectronics, Department of Engineering, National Science and Technology Council (NSTC), Taiwan
2023 – Present	***Review Committee Member***, Division of Biomedical Engineering, Department of Engineering, NSTC, Taiwan
2023 – Present	***Review Committee Member***, Division of Biomedical Engineering, Department of Life Sciences, NSTC, Taiwan
2022、2024	***National Innovation Award,*** Institute for Biotechnology and Medicine Industry, Taiwan.
2022	***Young Principle Investigator Awards,*** Taiwan Bio-development Foundation TBF*,* Taiwan, (only *two* Young Investigators, *with less than 50 years old*, are selected annually in research field of Biomedical Engineering)
2019-2023	***Ta-You Wu Research Grant for Distinguished Young Principle Investigators,*** Ministry of Science and Technology, Taiwan
2018	***Young Principle Investigator Awards in Medicine*** (青杏醫學獎)*,* Medical Science of Culture and Education Foundation(青杏文教基金會), Taiwan, (only *three* Young Investigators, *with less than 45 years old*, are selected annually among currently ~800 Principle Investigators in NTU medical school and NTU hospital.)
2016	***Ta-You Wu Memorial Award*** (吳大猷先生紀念獎) for Distinguished Young Principle Investigators*,* Ministry of Science and Technology (MOST), Taiwan, (only *one* Young Investigator, *with less than 42 years old*, is selected annually among ~1500 Principle Investigators in *Taiwan MOST Photonics Program and Society*.)
2016	***C.Y. Lee Memorial Foundation Award*** (李鎮源院長紀念醫學獎)*,* National Taiwan University College of Medicine, Taiwan, 2016. (only *two* Young Investigators, *with less than 42 years old*, are selected annually among currently ~400 Principle Investigators in NTU medical school.
2016-2018	***Young Principle Investigators' Award*** (年輕學者獎助計畫)*,* Ministry of Science and Technology, Taiwan,.
2013-2016	***Career Development Awarded CDG Research Grant,*** National Health Research Institute, Taiwan
2013	***Paper Award,*** Laser Medical Foundation, Taiwan
2009	***National Research Fellowship at MIT,*** National Science Council, Taiwan
2008	***Graduate Valedictorian,*** College of Optical Sciences, University of Arizona, USA
2008	***Achievement Award for Outstanding Research Assistant,*** Graduate and Professional Student Council (GPSC), University of Arizona, USA
2008	***Outstanding Graduate Student Award,*** College of Optical Sciences, University of Arizona, USA, 2008.

Advanced Metasurface Optics for Next-Generation Biomedical Technologies

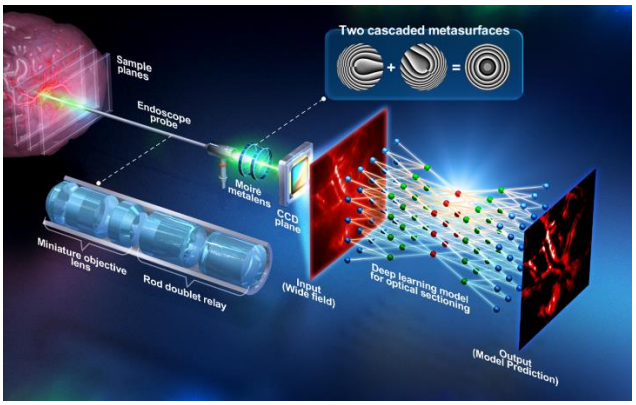
Yuan Luo
駱遠

Institute of Medical Device and Imaging, National Taiwan University, Taiwan

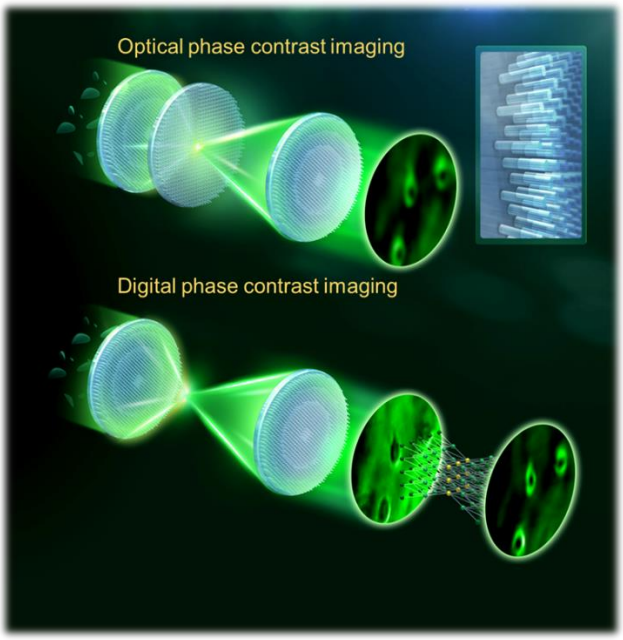
Metasurfaces ultrathin, planar optical structures engineered to manipulate light at the subwavelength scale have emerged as a transformative technology in the field of biomedical optics. Their ability to control wavefronts with high precision enables the design of compact, multifunctional optical components, including lenses, beam shapers, and polarizers, with unprecedented flexibility. This presentation explores recent advances in metasurface-based optical elements tailored for biomedical applications, such as high-resolution imaging, optical sensing, and minimally invasive diagnostics. By integrating these metasurfaces into biomedical systems, we can overcome traditional optical limitations, reduce device footprints, and enhance imaging performance. The talk will also highlight ongoing challenges and future directions in the development of scalable, biocompatible, and wavelength-tunable metasurface devices.



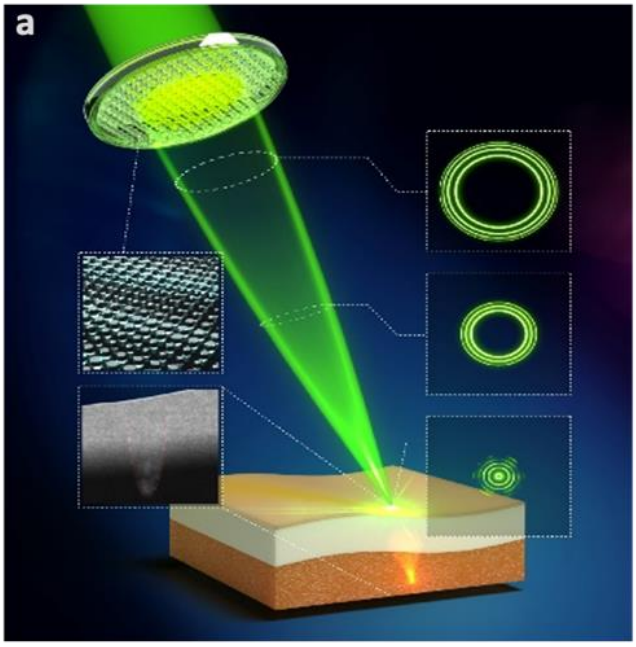
Moiré Tunable Lens



Varifocal Metalens for Endo-microscopy



Meta-miniscopy



Laser Treatment using Nano-photonics

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Education

1999-2004	Master's degree with honours, Theoretical Physics Department, Kaliningrad State University
2004-2007	Ph.D. degree in the Theoretical Physics Department, I. Kant State University, Kaliningrad

Research and Professional Positions Held in Chronological Sequence

2020-	Associate Principal Investigator, Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes
2015/02-	Head of the Laboratory: Biomedical Simulation Laboratory, National Health Research Institutes
2020-	Associate Professor (Joint Appointment), National Taiwan University, Department of Engineering Science and Ocean Engineering
2020-	Associate Professor (adjunct), National Chung Hsing University, Graduate Institute of Biomedical Engineering, Research Center in Tissue Engineering and Regenerative Medicine
2024/06-	Associate Professor (Joint Appointment), National Taiwan University, Department of Biomedical Engineering
2015/02-2019	Assistant Principal Investigator, Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes
2016/02-2019	Assistant Professor (Joint Appointment), National Taiwan University, Department of Engineering Science and Ocean Engineering
2016/09-2019	Assistant Professor (adjunct), National Chung Hsing University, Graduate Institute of Biomedical Engineering, Research Center in Tissue Engineering and Regenerative Medicine
2012-2015/02	Research Associate, National Taiwan University, Taida Institute for Mathematical Sciences (TIMS), Center for Advanced Study in Theoretical Sciences (CASTS)
2011-2012	Postdoctoral Research Fellow, National Taiwan University, Taida Institute for Mathematical Science (TIMS), Center for Advanced Study in Theoretical Sciences (CASTS)
2009-2011	Postdoctoral Research Fellow, National Taiwan University, Department of Engineering Science and Ocean Engineering

2008-2009	Associate Professor (Docent), Theoretical Physics Department, I. Kant State University
2005-2008	Assistant Professor of Theoretical Physics Department, I. Kant State University

Research Interests

1. High intensity focused ultrasound, nonlinear acoustics
2. High Performance Computing on multiple GPUs and CPUs, computational fluid dynamics
3. Machine Learning, thermal treatment of liver tumor: modeling, simulation and measurement
4. Statistical physics, kinetic gas theory, Boltzmann equation
5. Nano-channel flow modeling, ion channels
6. Multiphysics multiscale modeling for biomedical applications

Major Honors and Awards

2022	Outstanding Young Scholar Research Project Award, Ministry of Science and Technology
2022/08	Cover page of Nanoscale (journal published by Royal Society of Chemistry)
2022	Young Scientist Award, National Health Research Institutes
2022/01	Editor's Pick for paper in Physics of Fluids
2014	Paper in Journal of Computational Surgery – most read paper all time
2014/10	Young Investigator Award at 1st Global Conference on Biomedical Engineering (GCBME 2014) and 9th Asian Pacific Conference on Medical and Biological Engineering (APCMBE 2014), Tainan, Taiwan
2014	Best Paper Award at 21th National Computational Fluid Dynamics Conference, Taiwan, August 2014
2013	Best Research Paper Award for Young Researcher by National Science Council (now it is renamed as Ministry of Science and Technology)
2012	the paper was among Top 20 most download AIP papers in June, 2012
2012-2014	Who's Who in the World - 2013, 30th Edition and 2014, 31st Edition
2011	ICU grant to attend International Congress on Ultrasonics, Poland
2010	ICA Young Scientist Grant to attend 20th International Congress on Acoustics, Sydney
2006/09	The best report of a young researcher at the section “Atmospheric acoustic” at XVIII Session of the Russian Acoustical Society
2006-2007	Scholar of the President of the Russian Federation
2002-2004	Scholar of city administration
2001	Winner of the Olympiad among institutes of higher education (Universities) at Engineering Mechanics

High Performance Simulations on GPUs and AI for Treatment Planning of Radiofrequency Ablation of Liver Tumor

Maxim Solovchuk
馬克沁

Institute of Biomedical Engineering and Nanomedicine,
National Health Research Institutes, Taiwan

Liver cancer is one of the most common malignancies worldwide. Radio-frequency ablation (RFA) is minimally invasive treatment and is the second most common treatment modality after surgery for liver tumor in Taiwan. RFA is the thermal method for the ablation of tumors, which have certain benefits compared with conventional treatment modalities like open surgery, radio – and chemotherapy. Since liver has a large number of blood vessels, blood flow cooling can reduce the necrosed volume and may cause regeneration of the tumor to occur. It is quite difficult to achieve complete ablation of tumors close to major blood vessels and avoid damage of healthy organs, hence, the needed treatment planning. We are working on the development of the treatment planning platform for the thermal ablation of cancer. AI is used for automatic tumor detection and hepatic vessels and liver segmentation, which are used for the creation of the anatomical model. For the prediction of the treatment outcome mathematical and computational models have been constructed. Simulations in a patient specific geometry requires very long time, therefore High-Performance Computing on GPUs is used for the prediction of the treatment outcome and optimization of the treatment. The temperature elevation and necrosed area formation have been predicted and compared with ex-vivo experimental data in liver and very good agreement has been found. In addition, the results of numerical simulations and clinical treatment in about 15 patients have been compared and very good agreement was found.

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Education

1978-1985	M.D., School of Medicine, National Defense Medical Center, Taiwan

Research and Professional Positions Held in Chronological Sequence

1985-1990	Resident, Department of Radiology, Tri-Service General Hospital, Taiwan
1990-2011	Attending Neuroradiologist, Department of Radiology, Tri-Service General Hospital, Taiwan
1992-1993	Clinical Researcher, Department of Radiology, The Children Hospital's of Philadelphia, USA
2000-	Professor, National Defense Medical Center, Taiwan
2013-2014	Professor, Graduate Institute of Clinical Medicine, Taipei Medical University, Taiwan
2013-	Attending Neuroradiologist, Department of Medical Imaging, Taipei Medical University Hospital, Taiwan
2014-	Professor, Department of Radiology, College of Medicine, Taipei Medical University, Taiwan
2018-	Director, Translational Imaging Research Center, Taipei Medical University Hospital, Taiwan
2019-2023	Vice president, Taipei Medical University, Taiwan
2019-2023	Director, Center for Artificial Intelligence in Medicine, Taipei Medical University, Taiwan
2021-	Distinguished Professor, Department of Radiology, College of Medicine, Taipei Medical University

Research Interests

1. Mild traumatic brain injury (mTBI)
2. Ischemic stroke
3. Gliomas
4. Drug abuse
5. Dementia

Major Honors and Awards

1997	Scientific Exhibition, the second prize, The second Asian and Oceanian Congress of Neuroradiology and Head and Neck Radiology, Taipei, Taiwan

1999	Scientific Exhibition, the third prize, The Third Asian and Oceanian Congress of Neuroradiology and Head and Neck Radiology, Adelaide, Australia
2013	Scientific Exhibition, the third prize , European Society of Neuroradiology 37th Annual meeting, 2013, Frankfurt, Germany
2018	Magna Cum Laude, RSNA 2018-104th Scientific Assembly and Annual Meeting, 2018, Chicago, USA
2021-2023	2021, 2022, 2023 Future Tech Awards
2021-2024	2021, 2022, 2023, 2024 National Innovation Award
2023	National Biotechnology Research Park Pitch Day Outstanding Award
2024	2023 Outstanding Research Award, National Science and Technology Council
2024	American Society of Neuroradiology (ASNR) 2024 Honorary Member Award
2024	NBRP Pitch Day Potential Team Award
2024	Asia-Pacific Sustainability Action Awards- Gold
2024	Outstanding Contribution Award, Wang Ming-Ning Memorial Foundation
2025	A Foreign Honorary Member of the Japanese Society of Neuroradiology

From MR Imaging Biomarkers to Immunotherapy: A Translational Approach to Targeted Brain Cancer Treatment

Sandy, Cheng-Yu Chen,
陳震宇

Translational Imaging Research Center, Taipei Medical University Hospital, Taiwan
Department of Medical Imaging, Taipei Medical University Hospital, Taiwan
Department of Radiology, School of Medicine, Taipei Medical University, Taiwan

This lecture presents a comprehensive framework for integrating advanced MR neuroimaging with genomic analysis and immunotherapy in the management of malignant glioma. Glioblastoma (GBM) remains one of the most aggressive and treatment-resistant malignancies, with conventional therapies offering limited survival benefits. A critical yet underappreciated aspect of GBM biology is the peritumoral brain zone (PBZ), where 90% of recurrences occur within 2 cm of the resection margin. This region, often radiologically "normal" on conventional MRI, harbors infiltrative tumor cells, glioblastoma-associated stromal cells, and immunosuppressive myeloid populations that create a fertile microenvironment for recurrence. Over the past two decades, advanced MR imaging biomarkers have revolutionized our understanding of this invisible PBZ. From early morphologic assessments (T1/T2) to physiologic (DSC/DCE) and cellular (DWI/DKI) imaging, these tools now enable non-invasive characterization of PBZ biology. Particularly, radiogenomic mapping has revealed distinct imaging phenotypes associated with molecular alterations - EGFR-amplified GBMs show thicker PBZ enhancement, IDH-wildtype tumors exhibit infiltrative FLAIR patterns, and mesenchymal subtypes display restricted diffusion due to stromal infiltration. These advances allow virtual biopsies of the PBZ, guiding more precise therapeutic interventions. To translate these imaging insights into targeted therapies, we developed a theranostic platform combining superparamagnetic iron oxide (SPIO) nanoparticles with interleukin-19 (IL-19) antibodies. This approach addresses two fundamental challenges: detection and treatment of PBZ microinvasion. The CHOL-PEG-SPIO-IL19Ab nanoparticles serve a dual purpose - enhancing MRI detection of infiltrative cells through susceptibility artifacts at 7T MRI while simultaneously delivering targeted immunotherapy. Preclinical studies demonstrate these particles reduce PBZ tumor volume by 62% and extend survival by 40% compared to controls. The selection of IL-19 as a therapeutic target emerged from big data analysis of PBZ transcriptomes, revealing its role as a master regulator of immunosuppression. IL-19 is overexpressed in PBZ myeloid cells, inducing M2 polarization via STAT3 and correlating with shorter survival (HR=2.1, $p<0.001$) in TCGA-GBM datasets. Our phase 0 trial using SPIO-IL19Ab fluorescence imaging confirmed PBZ-specific IL-19 expression in 12/15 patients, validating its clinical relevance. The clinical translation of this work is now being advanced through three key aims. First, we are generating a humanized IL-19 antibody to investigate its effects on GBM migration, invasion, and proliferation, while assessing its ability to shift macrophages from pro-tumoral M2 to anti-tumoral M1 phenotypes. Second, comprehensive in vivo validation studies will evaluate intravenous and subcutaneous administration routes, analyze tumor microenvironment modulation via scRNA-seq in immune-humanized models, and assess toxicity, immunogenicity, and hemocompatibility of the nanoparticle system. These studies will also determine whether humanized IL-19 antibody enhances immune checkpoint blockade efficacy. Third, we are optimizing the IL-19-targeted theranostic nanoparticle system by improving targeting efficiency and blood-brain barrier penetration, while conducting pharmacokinetic, pharmacodynamic, and biodistribution studies to facilitate clinical translation. This multi-pronged approach represents a paradigm shift in GBM management, integrating advanced imaging biomarkers with nanotechnology and immunotherapy to address the fundamental challenge of PBZ-driven recurrence and move toward personalized, image-guided therapy for this devastating disease. Keywords: Glioblastoma, peritumoral brain zone, radiogenomics, IL-19, SPIO nanoparticles, tumor microenvironment, immunotherapy.

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China Medical University
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Phone No.: 04-2205-3366 ext. 7928
E-mail: ypsher@mail.cmu.edu.tw
Web: https://webap.cmu.edu.tw/TchEportfolio/index_1/ypsher

Education

1990-1994	B.S., Medical Technology, National Taiwan University, Taiwan
1994-1996	M.S., Medical Technology, National Taiwan University, Taiwan
2001-2006	Ph.D., Graduate Institute of Molecular Medicine, National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2007-2009	Postdoctoral Fellow, Center for Molecular Medicine, China Medical University Hospital
2009-2015	Assistant Professor, Graduate Institute of Clinical Medical Science, China Medical University
2015-2022	Associate Professor, Graduate Institute of Biomedical Sciences, China Medical University
2022-	Professor, Graduate Institute of Biomedical Sciences, China Medical University
2022-	Professor, The Ph.D. program for Cancer Biology and Drug Discovery, China Medical University
2023-	Director, Institute of Biochemistry and Molecular Biology, China Medical University

Research Interests

My research focuses on elucidating the critical mechanisms driving cancer metastasis across diverse malignancies, including lung cancer, triple-negative breast cancer, esophageal squamous cell carcinoma, and pancreatic cancer. Our integrated approach combines biochemical investigations, clinical data analysis, and preclinical mouse models to identify novel therapeutic targets and develop promising cancer treatments for clinical translation.

Major Honors and Awards

1997	Excellent Thesis Prize in Medical College of National Taiwan University
1998	Travel Award of the Institute of Biomedical Sciences, Academia Sinica
2001	Travel Award of the Institute of Biomedical Sciences, Academia Sinica
2007	NHRI Postdoctoral Fellowship Award
2011	The first place of poster competition in International Symposium on Translational Cancer Research in conjunction with the 15th Annual Meeting of the Taiwan Cooperative Oncology Group

2016	Award of Travel Grant of the 75th Annual Meeting of the Japanese Cancer Association
2020	The 17th National Innovation Award in the Academic Research Category
2022	The 19th National Innovation Excelsior Award in the Academic Research Category
2022	Boehringer Ingelheim’s Grass Roots Program (Cancer Therapies)
2024	Outstanding Research Awards in Category of Medical Biochemistry and Molecular Biology by NSTC

ADAM9 Inhibition Promotes KRAS Degradation in Pancreatic Cancer Treatment

Yuh-Pyng Sher
佘玉萍

Institute of Biochemistry and Molecular Biology, China Medical University, Taiwan

Pancreatic cancer presents a formidable challenge in therapeutic intervention due to the enduring resistance posed by KRAS signaling over the past three decades. The inherent diversity of KRAS mutations and the coexistence of multiple KRAS mutants within pancreatic tumors render targeting a single mutant type impractical. Our investigations have unveiled a distinctive ADAM9-KRAS loop that amplifies KRAS activity through a feed-forward mechanism. This unique signaling cascade, which accentuates the effects of KRAS in cancer cells while sparing normal cells, emerges as a viable targetable pathway for therapeutic design. Intriguingly, we have uncovered that ADAM9 translocates from the membrane into the nucleus and nuclear ADAM9 operates as a transcriptional repressor to maintain low levels of plasminogen activator inhibitor-1 (PAI-1). We describe endogenous plasminogen activator inhibitor 1 (PAI-1) as a novel selective autophagy receptor that eliminates KRAS proteins under stress. The up-regulated PAI-1 directly interacts with KRAS and LC3 to induce the lysosomal degradation of KRAS under ADAM9-depleted conditions. Significantly, our studies demonstrate that ADAM9 suppression augments KRAS degradation across pancreatic cancers harboring both wild-type and mutant KRAS. Notably, the development of ADAM9 inhibitors holds promise as pan-KRAS inhibitors capable of targeting diverse KRAS mutants, presenting a transformative approach to pancreatic cancer treatment (Nature Cancer, 2024). I will expound upon our research discoveries regarding ADAM9 and its profound implications in the realm of cancer therapeutics.

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E-mail: htsai@ntu.edu.tw
Web: http://tsailab.cm.ntu.edu.tw

Education

1992-1999	M.D., National Taiwan University, Taiwan
2002-2004	M.S., Graduate Institute of Clinical Medicine, National Taiwan Univ., Taiwan
2005-2011	Ph.D., Johns Hopkins University School of Medicine, USA

Research and Professional Positions Held in Chronological Sequence

1999-2002	Resident, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2002-2004	Clinical Fellow, Division of Chest Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2003-2004	Chief Resident, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2011-2014	Research Fellow, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, USA
2014-2022	Assistant Professor Graduate Institute of Toxicology, College of Medicine, National Taiwan University, Taipei, Taiwan
2014-present	Attending physician, Division of Chest Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2021-present	Deputy Director, NTUH Center for Frontier Medicine, National Taiwan University Hospital, Taipei, Taiwan
2022-present	Associate Professor Graduate Institute of Toxicology, College of Medicine, National Taiwan University, Taipei, Taiwan
2025-present	Joint Appointment Associate Research Fellow, Institute of Biomedical Sciences, Academia Sinica

Research Interests

Our research focuses on unraveling the intricate interplay between cancer cells and the tumor immune microenvironment from an epigenetics perspective. By bridging basic research,

translational medicine, and clinical applications, our goal is to develop innovative cancer immunotherapies and diagnostic strategies, ultimately leading to improved patient outcomes.

Our key research directions include:

- Epigenetic Regulation of the Tumor Immune Microenvironment — We investigate how epigenetic mechanisms shape the tumor immune microenvironment by regulating immune cell differentiation, activation, and dysfunction. Using a targeted drug screening platform, we have identified epigenetic compounds that restore polyfunctionality and plasticity in exhausted T cells. Our research explores the metabolic pathways underlying these effects and their broader impact on anti-tumor immunity. We also apply multi-omics approaches to characterize peripheral immune alterations in early-stage lung cancer, aiming to identify blood-based epigenetic biomarkers and develop strategies to restore systemic immune competence.
- γδ T Cell-Based Cancer Immunotherapy — Our lab develops γδ T cells for adoptive cellular immunotherapy, leveraging their HLA-independent tumor recognition and rapid cytotoxic activity. We have established a clinical-grade γδ T cell expansion protocol and are optimizing it for regulatory compliance. Concurrently, we study the molecular and synaptic mechanisms of γδ T cell-mediated tumor killing and are identifying predictive biomarkers of expansion efficiency and therapeutic potency. Our goal is to enable γδ T cell-based precision immunotherapies for clinical application.

Major Honors and Awards

2005	Taiwan Merit Scholarship, by Taiwan's Ministry of Education, Council for Economic Planning and Development, and National Science Council
2012	Honorable Mention for Basic Research, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
2016	Best oral presentation award, Annual Meeting of Pulmonary Critical Care Medicine, Taiwan Society of Pulmonary and Critical Care Medicine
2017	Young Investigator Outstanding Research Award, National Taiwan University Hospital（臺大醫院傑出研究獎）
2020	The ITRI 2020 Janssen-Taiwan Research Grant Awardee
2021	The 18th National Innovation Award（國家新創獎）
2022	The Ming Chai Medical and Education Foundation Interdisciplinary Research Award
2024	Fellow of the Asian Pacific Society of Respirology（亞太呼吸學會會士）

Rewiring Epigenetic and Metabolic Circuits to Enhance Cancer Immunotherapy

Hsing-Chen Tsai
蔡幸真

National Taiwan University College of Medicine, Taiwan

The dynamic interplay between cancer cells and the immune microenvironment plays a pivotal role in determining the balance between immune activation and evasion. While immunotherapies such as checkpoint blockade and adoptive cell transfer have shown significant promise, many patients still fail to achieve durable responses. Emerging evidence highlights epigenetic regulation as a key mechanism modulating both tumor immunogenicity and immune cell function, though its therapeutic potential in cancer immunotherapy remains underexplored. Our laboratory has demonstrated that epigenetic drugs can reprogram cytoskeletal and immune synapse structures in cancer cells, increasing their susceptibility to γδ T cell–mediated cytotoxicity. γδ T cells bridge innate and adaptive immunities and can recognize tumor cells in an MHC-independent manner, making them ideal candidates for both autologous and allogeneic adoptive cellular therapies. Additionally, we have identified epigenetic compounds capable of reinvigorating terminally exhausted T cells, restoring their plasticity and polyfunctionality. Notably, this reprogramming is closely linked to metabolic remodeling, particularly through activation of the polyamine biosynthetic pathway and elevated intracellular polyamine levels. This connection reveals a unique axis by which epigenetic perturbation can influence immune cell metabolism and function. Together, our findings underscore the potential of targeting epigenetic and metabolic pathways to enhance antitumor immunity. By bridging these regulatory networks, we aim to develop innovative therapeutic strategies that reshape the tumor immune microenvironment and improve the efficacy of cancer immunotherapy.

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National Institute of Cancer Research
National Health Research Institutes
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Fax No.: 037-586-463
E-mail: tailungcha@nhri.edu.tw

Education

1983-1990	M.D., School of Medicine, National Defense Medical Center
2000-2005	Ph.D., Molecular Cellular Oncology Department, University of Texas MD Anderson Cancer Center

Research and Professional Positions Held in Chronological Sequence

2021/6- present	Member of the Ministry of Education Diploma Review Committee for Grudates from Departments of Medicine, Departments of Dentistry, and Departments of Traditional Chinese Medicine in Foreign Universities
2021/8-2024/7	Member of the 8th Taiwan Medical Accreditation Council
2022/1-2022/12	Convener of the Division of Nephrology, Urology, and Endocrine Medicine, Department of Life Sciences, Ministry of Science and Technology
2022/9-2026/8	11th Director of Cheng Hsin Medical Foundation
2022/11-2025/11	Executive Director of the Taiwan Association of Medical Education
2023/1-2023/12	Convener of the Division of Nephrology, Urology, and Endocrine Medicine, Department of Life Sciences, National Science and Technology Council
2023/2-2026/2	Supervisor at the Institute for Biotechnology and Medicine Industry
2023/1-2023/12	Member of the 25th Appointment Qualification Review Committee of National Health Research Institutes
2023/2-2026/1	Honorary Consultant at the Center for Biomedical Engineering in Cancer, Chung Yuan Christian University
2023/5-2024/12	Municipal Advisor, Taipei City Government
2024/8- present	Distinguished Investigator, Director, National Institute of Cancer Research, National Health Research Institutes

Research Interests

Oncology, surgical oncology, cancer metastasis, cancer immunology, anticancer drug development, genitourinary diseases, urology

Major Honors and Awards

2005/11/11	Featured research article published in Science
2005-2009	Sponsored Physician under the Subsidy Program for Healthcare

	Professionals in Medical Institutitons to Conduct Clinical Research by the Formosa Cancer Foundation
2006/11/24	Received the 2006 Excellent Military Doctor Award/ Received the Excellent Academic Paper Award
2006/1	Won 1st place at the International Society of Surgery Academic Paper Awards
2006/3	Won 1st place at the Taiwanese Association of Andrology Paper Awards
2008	Won 3rd place in the 2008 Taiwan Urological Association Journal Paper Group Competition
2009	Won 1st place in the 2009 Taiwan Urological Association Journal Paper Group Competition
2009	Received the 16th Taiwan Urological Association MSD Research Award in the Basic Research Division
2009	Received the 2009 Excellent Military Doctor Award
2009	Member of the On-Site Review Commitee for the Research Exhibition of the 36th National Military Medical Symposium
2010	Won 5th place at the 2010 National Doctor's Day and Military Medical Conference Excellent Treatise Awards
2011	Received the 2011 ROC Armed Forces Excellent Medic Award
2012	Received the 2012 National Defense Medical Center Excellent Teacher Award
2016	Received the 2016 National Innovation Award in the Biotechnology and Pharmaceutics Division of the Academic Research and Innovation Category
2017	Received the 2017 Residential Kyorin Award by Taipei Medical Association
2021	Received the 2021 National Excellent Teacher Award of the Ministry of Education
2022	Listed in the World's Top 2% Scientists 2021

Uncovering Atypical GPCR Pathway Mediates Cell-intrinsic Adaptation and Extrinsic Communication Contributing to Cancer Progression

Tai-Lung Cha
查岱龍

National Institute of Cancer Research, National Health Research Institutes, Taiwan
Tri-Service General Hospital, National Defense Medical Center, Taiwan

Cancer progression is shaped by both cell-intrinsic adaptations and complex extrinsic interactions within the tumor microenvironment (TME). Here, we identify a transmembrane protein, Meta1, as a shared therapeutic target that exhibits a Janus-like role: promoting malignant phenotypes in cancer cells while restraining tumor-supportive functions in non-cancerous stromal and immune cells. Meta1 is expressed in both compartments of the TME, orchestrating a dual program that supports metastasis and immune evasion. Mechanistically, we uncovered a metastasis-promoting factor (MPF) that acts as a functional ligand for Meta1, selectively enhancing pro-invasive signaling in cancer cells. We further identify Meta1 as an unconventional G protein–coupled receptor (GPCR) that plays a Janus-like role—functioning as an accelerator in cancer cells and a brake in non-malignant cells of the TME. Meta1 interacts with Rho-GDI and Gαq to activate RhoA-mediated cytoskeletal remodeling and amoeboid migration, facilitating metastatic dissemination. We further identify MPF binding to Meta1 initiates Gβγ signaling, elevating intracellular cAMP and activating Rap1, thereby amplifying cell motility and metastatic potential. Leveraging the Meta1–MPF interaction, we designed MPF-derived peptides that specifically bind Meta1 and serve as the basis for a novel peptide-based PROTAC, which efficiently induces degradation of Meta1 and abrogates its pro-metastatic functions. Our study unveils Meta1 as an atypical GPCR with canonical signaling capacity and topological divergence, representing a shared and targetable vulnerability that bridges cancer cell-intrinsic adaptation with extrinsic TME communication. These findings establish the Meta1–MPF axis as a compelling therapeutic target for suppressing metastasis and reprogramming the TME.

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https://www.webofscience.com/wos/author/record/P-4726-2017

Education

1981-1988	Doctor of Medicine, Chung Shan Medical University, Taiwan
1998-2001	Post-doctoral Fellow, Department of Epidemiology and Public Health, Yale University, Graduate School of Arts and Sciences, U.S.A.
2001	Doctor of Philosophy
2002-2004	Executive Master of Business Administration in International Business, College of Management, National Taiwan University

Research and Professional Positions Held in Chronological Sequence

1988-1992	Resident and Chief Resident, Dept. of Psychiatry, NTUH, Taipei, Taiwan
1992-present	Senior (Child) Psychiatrist, Dept. of Psychiatry, NTUH, Taipei, Taiwan
1996-2002	Lecturer, Department of Psychiatry, NTU College of Medicine, Taiwan
2001-2005	Director, Student Counseling Center, National Taiwan University, Taiwan
2002-2005	Assistant Professor, Department of Psychiatry, National Taiwan University Hospital, College of Medicine, Taiwan
2009-2018	Chairperson, Dept. of Psychiatry (2009-2015), Dept. of Medical Genetics (2015-2018), NTU Hospital & College of Medicine.
2005-2009	Associate Professor,
2009-present	Professor, Dept. of Psychiatry of School of Medicine, School of Occupational Therapy, Dept. of Psychology, Graduate Institute of Epidemiology and Preventive Medicine, Graduate Institute of Brain and Mind Sciences, Graduate Institute of Clinical Medicine, NTU, Taiwan.
2020-present	Vice Superintendent, National Taiwan University Hospital, Taipei, Taiwan.
2023-present	President, Taiwan Medical Women's Association
2023-present	Convener, Mental Illness Prevention and Treatment Advisory Council, Ministry of Health and Welfare
2023-present	Director, Board of Directors, National Atomic Research Institute
2023-present	Distinguished Professor, Dept. of Psychiatry, National Taiwan University Hospital & College of Medicine, National Taiwan University, Taiwan.
2024-present	Member, Healthy Taiwan Promotion Committee
2024-present	Head, Division of Child Psychiatry, Dept. of Psychiatry, NTUH, Taiwan

Major Honors and Awards

1993	National Taiwan Hospital Residency Research Award

1997	Three-Year Scholarship from the Ministry of Education, Taiwan
2001	Dissertation with Honors, Yale University School of Medicine
2002	Young Investigator Award, American Neuropsychiatric Association
2004	Travel Award, International Federation of Psychiatric Epidemiology Teaching Excellence Award, National Taiwan University, Taiwan National Award of Excellence in Leadership of Student Counseling of College
2007	Award of Excellent Performance in Medicine, Chin-Shin Foundation, National Taiwan University College of Medicine Outstanding Paper Presentation Award of the Taiwanese Society of Psychiatry
2011	AACAP Outstanding Mentor Award for mentoring Jessica Chuang in the Summer -Medical Student Fellowship in Child and Adolescent Psychiatry.
2012	Outstanding Research Award of National Science Council
2013	Distinguished Research Award of National Taiwan University
2014	Grant awards for three projects across 14 years from National Health Research Institute, Taiwan.
2015	Academic Excellence Award, the 108 annual meeting of Formosan Medical Association
2016	National Taiwan University Hospital Outstanding Research Award
2018	The Best Clinical Teacher awarded by National Taiwan University College of Medicine Alumni Association in North America (NTUMCAA-NA). National Taiwan University Teaching Excellence Award
2019	National Taiwan University Hospital Outstanding Research Award (ADHD Consortium) Teaching Excellence Award
2020	Physician Model Award, Taiwan Medical Association
2020	IACAPAP Medal for Outstanding Contribution By the International Association of Child and Adolescent Psychiatry and Allied Professionals
2021	Advancing Curiosity Award, Micron Foundation
2021	Wang Ming-Ning Award in Outstanding Contribution to Clinical Medicine, WANG MING-NING MEMORIAL FOUNDATION
2022	Outstanding Paper Award of the 61st Annual Meeting of the Taiwan Society of Psychiatry (Corresponding author)
2022	Special Contribution Award for COVID-19 Prevention, Taiwan Medical Association
2023	Medical Human Rights Contribution Award, Chinese Association for Human Rights
2024	21st National Innovation Award 「AQ-13: The Next Generation AI-Powered Screening and Auxiliary Diagnosis for Autism」
2024	2023 Outstanding Research Award from the National Science and Technology Council
2023-2025	Hung Lu Outstanding Paper Award from the Taiwanese Society of Child and Adolescent Psychiatry

Multimodal Characterization of Autism:

Integrating Cognitive, Neuroimaging, and Gut–Brain Axis Data

Susan Shur-Fen Gau
高淑芬

Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taiwan

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with diverse clinical and genetic characteristics. Our autism research began with developing diagnostic instruments and questionnaires to assess clinical symptoms and social functions. Genetic studies explained only 5% of the variance in our autistic population. We then collected multi-dimensional data from individuals with ASD, their unaffected siblings, and typically developing controls (TDC), including clinical, genetic, neuropsychological, imaging, microbiome, and metabolomics data.

Our research has characterized ASD based on imaging endophenotypes, genetic images, longitudinal studies, and metagenomic profiles. Our findings suggest potential endophenotypic markers for ASD, including verbal and spatial working memory, neuroanatomy, white-matter tract integrity, and intrinsic functional connectivity (iFC). Longitudinal data show that despite improvements in attention and executive functions, autistic individuals still have impairments in focused attention, cognitive flexibility, and visual memory compared to TDC at follow-up. Longitudinal iFC results indicate a relationship between atypical development of frontoparietal structural connections and ASD phenotype dynamics. Our normative model of diffusing spectrum imaging has been used to compare white matter tract deviations in ASD, ADHD, and their unaffected siblings and to test the neurodevelopmental model of schizophrenia.

Regarding metagenomic profiles, our research supports different patterns of the gut-microbiome-metabolomics-brain-behavior axis in ASD, unaffected siblings, and TDC. It identifies potential microbiomes for developing a probiotic treatment for ASD. Our ongoing project aims to advance precision health in ASD by identifying biomarkers, examining probiotic efficacy, and creating an artificial intelligence platform.

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Education

2004-2010	Ph.D., Graduate Institute of Epidemiology, College of Public Health, National Taiwan University

Research and Professional Positions Held in Chronological Sequence

2012-2016	Assistant Professor, Institute of Clinical Medicine, National Yang-Ming University
2016-2020	Associate Professor, Institute of Clinical Medicine, National Yang-Ming University
2020-2021	Professor, Institute of Clinical Medicine, National Yang-Ming University
2021-	Professor, Institute of Clinical Medicine, National Yang Ming Chiao Tung University
2021-2022	Leader, Planning Section, Office of Research and Development, National Yang Ming Chiao Tung University
2022-	Deputy Dean of Research and Development, National Yang Ming Chiao Tung University

Research Interests

Hepatobiliary tract diseases, metabolic dysfunction-associated steatotic liver disease, genetic epidemiology, and large-scale data analytics for precision medicine

Major Honors and Awards

2011	Professor Kung-Pei Chen Memorial Award
2011	Wang Ming-Ning Award, Wang Ming-Ning Memorial Foundation
2012	Young Investigator Award, Asian Pacific Association for the Study of the Liver
2013	Professor Sung Juei-Low's Academic Prize for Excellent Research
2013	Award for Outstanding Contributions in Science and Technology, Executive Yuan
2016	Ten Outstanding Young People
2020	Tien-Te Lee Award-Youth Medical Technology Award
2021	Outstanding Research Award, Ministry of Science and Technology

Shaping Hepatocellular Carcinoma Risk:
From Viral Etiologies to Metabolic Dysfunction and Beyond

Mei-Hsuan Lee
李美璇

National Yang Ming Chiao Tung University , Taiwan

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality worldwide. In Asian populations, HCC has traditionally been driven by chronic hepatitis B and C virus (HBV and HCV) infections. However, with widespread implementation of antiviral therapies and vaccination programs, the impact of viral hepatitis is gradually declining. Concurrently, the global rise in obesity, diabetes, and metabolic syndrome has contributed to the growing burden of metabolic dysfunction-associated steatotic liver disease (MASLD), now recognized as a major non-viral driver of liver-related morbidity and mortality. This presentation highlights findings from our recent population-based and genomic studies examining the evolving etiologic landscape of HCC. While chronic viral hepatitis remains a dominant risk factor, MASLD has emerged as a significant contributor to cirrhosis and HCC, especially among individuals without HBV or HCV infection. We further demonstrate that elevated liver enzyme levels—particularly in MASLD—serve as early indicators of liver cancer risk and are also associated with increased cardiovascular, diabetes, and all-cause mortality, underscoring MASLD as a multisystem disease. Drawing from large-scale community and nationwide data in Taiwan, a setting with high prevalence of both viral hepatitis and MASLD, we explore comparative risks and systemic implications. Beyond descriptive risk assessment, we present novel HCC prediction models for non-cirrhotic MASLD patients and evaluate the role of genetic variants, including *PNPLA3* and *SAMM50*, in enhancing individualized risk stratification. Finally, we extend the discussion to cholangiocarcinoma—an anatomically and etiologically related malignancy—where metabolic and lifestyle factors may similarly shape cancer susceptibility. Together, these findings call for a paradigm shift in liver cancer prevention, moving beyond viral eradication toward integrated metabolic risk management and precision surveillance strategies for at-risk populations.

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Education

1981-1985	BS, Rehabilitation Medicine, National Taiwan University, Taiwan
1988-1989	MS *with distinctions*, Occupational Therapy, Boston University, USA
1989-1994	ScD *with distinctions*, Therapeutic Studies, Boston University, USA

Research and Professional Positions Held in Chronological Sequence

1994 - 1996	Assistant Professor, Department of Occupational Therapy, Boston University Sargent College, Boston, MA, USA
1996 - 1997	Adjunct Assistant Professor, Department of Occupational Therapy, Boston University Sargent College, Boston, MA, USA
2000	Visiting Scholar, Department of Neuropsychology, Graduate Institute of Medicine, Tohoku University, Sendai, Japan
2008 - 2010	President, Taiwan Occupational Therapy Association
2011- Present	Adjunct Professor, Department of Occupational Therapy and Graduate Institute of Behavioral Sciences, Chang Gung University
2007 - Present	Chair, School of Occupational Therapy, College of Medicine, National Taiwan University, Taipei, Taiwan
2009 - Present	Professor, School of Occupational Therapy, College of Medicine, National Taiwan University, Taipei, Taiwan

Research Interests

Professor Keh-chung Lin is tenured Professor in occupational therapy at National Taiwan University. He obtained his ScD with distinctions in Therapeutic Studies in 1994 from Boston University, USA. Professor Lin was inducted to the distinguished US Academy of Research in Occupational Therapy in 2017 in recognition of his scholarly achievements. Professor Lin was awarded with Top 2% Scientists in the World by Stanford University in 2022, 2023, and 2024 to acknowledge the impact of his research.

Professor Lin has been devoted to research on stroke rehabilitation and teaching in higher education for the occupational therapy professionals for 30 years. His research work focuses on contemporary stroke rehabilitation, such as robotic therapy, mirror therapy, augmented reality, and hybridized interventions. To ensure that the patient and others can have confidence in the progress reported to them, Professor Lin has studied the reliability and responsiveness of tests that are used

to measure improvement in cognition, functional movement, self-efficacy and activities of daily living in persons with stroke. He has received 4 research grants from the National Health Research Institutes and published more than 240 research papers in peer-reviewed journals. Professor Lin is Associate Editor, Section Neurorehabilitation, of Frontiers in Neurology. Rehabilitation Robots, Neuropsychology, Meta-Analysis, Motor Control.

Major Honors and Awards

1991	Anne Henderson Scholarships, Boston University
1996-2001	Research Award, National Science Council, Taiwan
2000	The Gonryo Medical Award, Tohoku University, Japan
2000-2003, 2005-2013	Excellent Teaching Award, National Taiwan University
2002-2013	Marquis Who's Who in the World, New Providence, NJ, USA
2004-2006	Outstanding Intellectuals of the 21st Century, International Biographical Centre, Cambridge, UK
2006	Award for Excellent Innovative Teaching Material, National Taiwan University Hospital
2010	Excellent Research Paper Award, Taiwan Occupational Therapy Association
2011-2013	Outstanding Research Paper Award, National Taiwan University
2012	The 2012 Medical Science Award of Excellent, American Biographical Institute
2012-2013	The International Biographical Centre Cambridge Certificate for Outstanding Medical Achievement

An Update of Research Progress in Stroke Rehabilitation

Keh-chung Lin
林克忠

School of Occupational Therapy, College of Medicine, National Taiwan University and Division of Occupational Therapy, Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taiwan

Stroke is a leading cause of disability and the demand for rehabilitative intervention is growing. Remarkable advances have been made over the past two decades in stroke treatments to improve neurological outcome. Rehabilitation practices continue to help stroke patients regain functional independence. Substantial advances are yet to be made in stroke rehabilitation research. A number of promising research directions have been identified for rehabilitative interventions. Research grants funded by the National Health Research Institutes have promoted the investigator's work in pursuing these directions over the past 15 years. This current presentation will provide exemplary updates of the research progress. Prioritized agendas of the research program include outcome evaluations, favorable clinical studies, rehabilitation technology and predictive study of treatment outcome. Progress on the research endeavors will be the focus of this update. In the light of the progress, stroke rehabilitation research will strive for better interventions and outcomes.

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Education

1992	B.S., Mathematics, Fu-Jen Catholic University, Taiwan
1994	M.S., Mathematics, Fu-Jen Catholic University, Taiwan
2002	M.A., Mathematical Statistics, University of Maryland, College Park, USA
2005	Ph.D., Mathematical Statistics, University of Maryland, College Park, USA

Research and Professional Positions Held in Chronological Sequence

2005-2008	Post-doctoral Fellow, National Health Research Institutes, Taiwan
2008-2013	Assistant Investigator, National Health Research Institutes, Taiwan
2013-2024	Associate Investigator, National Health Research Institutes, Taiwan
2014-2024	Associate Professor, Graduate Institute of Biostatistics, College of Public Health, China Medical University, Taiwan
2015-present	Associate Editor, Journal of Biopharmaceutical Statistics
2015-present	Statistical Advisory Board, PLOS ONE
2024-present	Investigator, National Health Research Institutes, Taiwan
2024-present	Professor, Graduate Institute of Biostatistics, College of Public Health, China Medical University, Taiwan

Research Interests

Dr. Hsiao-Hui Tsou (Sophie) is a mathematical statistician with a PhD in Mathematical Statistics from the University of Maryland, College Park (2005). Her initial research focused on the design and analysis of clinical trials, encompassing bridging studies, multi-regional and biosimilar trials, and non-inferiority designs. Her extensive experience spans various therapeutic areas, including oncology, geriatric care, mental health, and substance abuse. Notably, Dr. Tsou also possesses expertise in evaluating the cost-effectiveness of public health interventions.

Aligning with the National Health Research Institutes' (NHRI) mission, Dr. Tsou specializes in applying mathematical and statistical models to understand and combat infectious diseases, including COVID-19 and dengue fever. She played a role in the "Comprehensive mosquito-borne disease control program" (2016-2021), contributing to database development, systematic data quality assessment, statistical analyses of dengue data, and providing insights for central and local epidemic prevention efforts. Her collaborative work resulted in the development of real-time dengue forecast models for outbreak alerts in Southern Taiwan, in partnership with the Kaohsiung

City Government. She also assisted colleagues in developing a SEIR model to understand dengue virus transmission dynamics.

Since the early stages of the COVID-19 pandemic (January 2020), Dr. Tsou has been instrumental in establishing mathematical models for the disease. As a member of the NHRI COVID-19 working group, she utilized stochastic transmission models to evaluate the effectiveness of contact tracing and case isolation. Her development of SEIR models based on dynamic ordinary differential equations provided critical predictions of COVID-19 spread. Over three years, under the leadership of NHRI's president, she collaborated closely with Taiwan's Centers for Disease Control (CDC), presenting dynamic model simulations at the Central Epidemic Command Center (CECC). These timely reports directly informed policymaking and enabled proactive public health measures.

Currently, Dr. Tsou leads the development of an Infectious Diseases Theme Database leveraging artificial intelligence (AI) to advance precision health. Furthermore, she applies big data analytics to infectious disease surveillance and modeling, incorporating human behavior data to assess the effectiveness and outcomes of COVID-19 policies.

Major Honors and Awards

2022	Service Contribution Award
2023	FutureTech Award. Topic: Application of natural language technology to build AI automation to manage infectious disease pathogen thematic database
2023	FutureTech Award.Topic: Establishing dynamic models to evaluate the mode of transmission and epidemic prevention measures for COVID-19

A Continuous Learning Journey:
From Clinical Trial Design to Infectious Disease Modeling and Public Health Impact

Hsiao-Hui Tsou
鄒小蕙

Institute of Population Health Sciences, National Health Research Institutes, Taiwan

This talk chronicles a continuous learning journey, illustrating the evolution of statistical and epidemiological methodologies from rigorous clinical trial design to dynamic infectious disease modeling, and their profound impact on public health policy. The journey commences with an exploration of Multi-Regional Clinical Trials (MRCTs), specifically focusing on methods for assessing the consistency of treatment effects using discrete random effects models. We will then present an example of a cancer clinical trial for prophylactic antiviral therapy, including its comprehensive cost-effectiveness analysis.

The narrative subsequently transitions to the realm of infectious diseases, beginning with the Dengue Fever Project. This section will showcase the development of real-time dengue forecasting for outbreak alerts. We will discuss the application of a Susceptible-Exposure-Infection-Recovery (SEIR) disease transmission model to simulate dengue virus transmission under various outbreak scenarios. By comparing these model simulations against real-world data from the 2015 Kaohsiung City dengue fever outbreak, we aim to elucidate the potential reasons for the rapid community spread that led to epidemics.

Further extending into broader public health impact, the talk will detail the development of infectious disease transmission models, particularly in the context of COVID-19. This includes assessing the impact of different screening times on infection rates, work that provided scientifically-based screening plans to the government, thereby facilitating the formulation of efficient screening schedules and flexible adjustments to home quarantine durations. We will also cover the assessment of various factors, such as vaccine protection, vaccine coverage, and breakthrough infections, on the risk of infection, alongside estimations of cases and severe hospitalizations in Taiwan.

Finally, the presentation will highlight collaborative efforts, including the proposal of a new index for comprehensive evaluation of COVID-19 policies and outcomes across 50 countries, and an analysis of the relationship between excess mortality and containment performance during the COVID-19 pandemic across 34 countries. The discussion will underscore the practical implications and significant contributions of these models to public health decision-making.

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Graduate Institute of Physiology, College of Medicine
National Taiwan University
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E-mail: linsl@ntu.edu.tw
Web: https://physiology.mc.ntu.edu.tw/Faculty/Faculty?id=25&openid=2

Education

1985-1992	B.M., Taipei Medical University, Taiwan
1997-2004	Ph.D., National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

1997-1999	Visiting Staff, Renal Division, En-Chu Kong Hospital, New Taipei City
1999-	Visiting Staff, Renal Division, National Taiwan University Hospital, Taipei
2003-2010	Assistant Professor, National Taiwan University College of Medicine, Taipei
2010-2015	Associate Professor, National Taiwan University College of Medicine, Taipei
2015-	Professor, National Taiwan University College of Medicine, Taipei
2016-2022	Director, Division of Blood Purification, Department of Integrated Diagnostics &Therapeutics, National Taiwan University Hospital, Taipei
2016-2022	Deputy CEO, Research Center for Developmental Biology and Regenerative Medicine, National Taiwan University, Taipei
2023/08-	Distinguished Professor, National Taiwan University College of Medicine, Taipei
2024/08-	Director, Department and Graduate Institute of Physiology, National Taiwan University College of Medicine, Taipei

Research Interests

1. Organ fibrosis; 2. Pericytes; 3. Macrophages; 4. Acute kidney injury; 5. Chronic kidney disease; 6. Erythropoiesis

Major Honors and Awards

2011	Chin-Hsin Medical Award, National Taiwan University College of Medicine, Taiwan
2016	Outstanding Research Award, Ministry of Science and Technology, Taiwan
2017	Outstanding Research Award, National Taiwan University, Taiwan
2019	Outstanding Research Award of Prof. Wan-Yu Chen Fund, Taiwan Society of Nephrology, Taiwan
2022	Outstanding Research Award, National Taiwan University Hospital
2022	Outstanding Research Award, National Science and Technology Council
2023	Wang Ming-Ning Award for Basic Science, Wang Ming-Ning Foundation

Pericyte-specific Targeting for Kidney Disease and Complication

Shuei-Liong Lin
林水龍

Department and Graduate Institute of Physiology, College of Medicine,
National Taiwan University, Taiwan

Pericytes are interstitial mesenchymal cells found in many major organs. In the kidney, microvascular pericytes are defined anatomically as extensively branched collagen-producing cells in close contact with endothelial cells. Although many molecular markers have been proposed, none of them can identify the pericytes with satisfactory specificity or sensitivity. The roles of microvascular pericytes in kidneys were poorly understood in the past. Recently, by using genetic lineage tracing to label collagen-producing cells or mesenchymal cells, the elusive characteristics of the pericytes are illuminated. In the healthy kidney, pericytes are found to take part in the maintenance of microvascular stability. Detachment of the pericytes from microvasculature and loss of close contact with endothelial cells are observed upon kidney injury. Kidney pericytes are shown to be the major source of scar-forming myofibroblasts in progressive kidney disease. Targeting the crosstalk between pericytes and neighboring endothelial cells or tubular epithelial cells may inhibit the pericyte-myofibroblast transition, prevent peritubular capillary rarefaction, and attenuate kidney fibrosis. In addition, kidney pericytes produce erythropoietin in healthy kidneys by sensing the change of oxygenation and hemoglobin concentration. However, the ability of erythropoietin production decreases in pericytes-derived myofibroblasts in chronic kidney disease, leading to renal anemia. Recent advances on epigenetics create a new field to study erythropoietin gene expression at chromatin level. Demethylating agent has shown the restoration of erythropoietin expression as well as downregulation of α smooth muscle actin in myofibroblasts. Through this talk I would like to share the knowledge in the physiology and pathophysiology of kidney pericytes, and our recent research on pericyte-specific drug delivery for kidney disease and complication.

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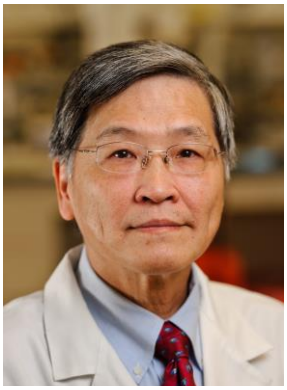

Education

1975 - 1982	M.D., National Yang-Ming Medical School
1984 - 1986	M.S., National Taiwan University, School of Medicine
1986 - 1990	Ph.D., Department of Physiology, School of Medicine, The Johns Hopkins University

Research and Professional Positions Held in Chronological Sequence

1980 - 1982	Internship, Veteran General Hospital, Taipei, Taiwan R.O.C.
1982 - 1984	Surgeon Officer and Lieutenant Officer, R.O.C. Army
1984 - 1986	Teaching Assistant, Department of Physiology, National Yang-Ming Medical College
1990 - 1993	Postdoctoral Associate, Laboratory of Cardiac/Membrane Physiology, The Rockefeller University
1993 - 1994	Assistant Professor, Laboratory of Cardiac/Membrane Physiology, The Rockefeller University
1994 - 1999	Assistant Professor, Department of Physiology, University of Missouri-Columbia
1994 -	Research Investigator, Dalton Cardiovascular Research Center
1999 - 2004	Associate Professor, Department of Physiology, University of Missouri-Columbia
2001 – 2002	Visiting Professor, Department of Physiology and Biophysics, Cornell Medical School
2004 - 2019	Professor, Department of Medical Pharmacology and Physiology, University of Missouri
2008 – 2009	Visiting Professor, Institute of Biophotonics, National Yang Ming University
2014 - 2017	Adjunct Professor, Kaohsiung Medical University
2019 -	Professor Emeritus, Department of Medical Pharmacology and Physiology, University of Missouri
2019 -	Adjunct Professor, Department of Medical Pharmacology and Physiology, University of Missouri
2019 - 2020	Professor, Department of Pharmacology, National Yang-Ming University
2019 - 2021	Consultant, Translate Bio Inc.

2019 -	Council Member, Gerson Lehrman Group
2019 - 2022	Consultant, Nanova Inc.
2019 -	Professor, Department of Pharmacology, National Yang Ming Chiao Tung University

Major Honors and Awards

1984	Service Award by R. O. C. Army
1986 - 1990	Scholarship, Ministry of Education, ROC
1986 - 1990	Fellowship, Department of Physiology, The Johns Hopkins University
1989	FASEB Award, Cell and General Physiology, American Physiological Society
1990	Certificate of Merit, Young Investigator Day, The Johns Hopkins University
1991 - 1994	Ella Fitzgerald Research Fellowship, New York Heart Association
1998	Excellence in Medical Student Education, MU Medical School.
1999	Excellence in Medical Student Education, MU Medical Student Affair Council.
2000	Professor-for-a-Day, School of Engineering, University of Missouri
2000	Paul Cranefield Award, Society of General Physiologists
2001	Excellence in Medical Student Education, MU Medical School
2001	Service Award, American Medical Student Association, University of Missouri
2001	Order of Socrates, MU Medical School
2007	Honorary Visiting Professorship, Osaka Medical College, Japan
2008	Visiting Professorship, Harbin Medical University, China
2009	Outstanding Alumni Award, National Yang Ming University, Taiwan
2010	Kwan-Hwa Honorary Professorship, Xian JiaoTong University, School of Medicine
2011	1st place poster award, Gordon Research Conference (with Yonghong Bai)
2015	Top Achiever, University of Missouri-Columbia
2017	Citation for Distinguished Service, Journal of General Physiology
2018	The Jack Riordan and Paul Quinton CF Science Award

Structure/Function Mechanisms of CFTR Modulators

Tzyh-Chang Hwang
黃自強

Institute of Pharmacology, National Yang Ming Chiao Tung University, Taiwan

CFTR is an epithelial chloride channel that plays a critical role in the secretion and reabsorption of salt and water. Loss-of-function mutations in CFTR are the underlying cause of cystic fibrosis (CF), the most common fatal genetic disease among Caucasians. Conversely, CFTR hyperactivity leads to secretory diarrhea, a major cause of mortality, particularly in developing countries. Therefore, developing agents that can modulate CFTR function—either by stimulation or inhibition—holds significant clinical potential. The discovery of ivacaftor, a CFTR potentiator, in 2008 has notably improved the quality of life for patients with CF.

In this presentation, I will first discuss our recent cryo-EM studies of the CFTR inhibitor CFTRinh-172. The atomic structure of the CFTR/CFTRinh-172 complex reveals a novel two-step inhibitory mechanism: first, CFTRinh-172 binds within the internal vestibule of the pore, blocking chloride permeation; second, this binding induces conformational changes that further obstruct the narrow region of the pore. I will present single-channel kinetic data that support this structure-derived mechanism. Furthermore, our findings suggest that this inhibitory mechanism may be applicable to structurally distinct compounds.

I will also share our latest results on the cryo-EM structures of CFTR in complex with new CFTR potentiators. These unpublished data offer new insights for structure-based drug design, aimed at developing more potent and effective therapeutics—not only for CF, but also for chronic idiopathic constipation, a prevalent condition among the elderly and a significant risk factor for colon cancer.

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National Taiwan University
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E-mail: suyitsai@ntu.edu.tw

Education

1998-2000	M.S., National Taiwan University, Taiwan
2006-2011	Ph.D., Icahn School of Medicine at Mount Sinai, USA

Research and Professional Positions Held in Chronological Sequence

2011-2012	Postdoctoral fellow, Icahn School of Medicine at Mount Sinai, Department of Developmental & Regenerative Biology, USA
2012-2015	Postdoctoral fellow, Weill Cornell Medical College, Department of Surgery, USA
2016-2020	Assistant Professor, National Taiwan University, Department of Life Science, Taiwan
2020-2024	Associate Professor, National Taiwan University, Department of Life Science, Taiwan
2024-present	Professor, National Taiwan University, Department of Life Science, Taiwan

Research Interests

My research group primarily utilizes human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) as a model system to investigate cardiac development and disease mechanisms. Our key achievements include establishing a robust platform for modeling human cardiac development and disease, and validating a system for studying human sarcomere assembly. Through this platform, we aim to uncover the molecular pathways underlying cardiomyopathies and identify potential therapeutic targets.

Major Honors and Awards

2015-2016	FFPI Postdoctoral fellowship, Weill Cornell Medical College, New York, USA. 2015-2016
2016-2019	MOST Special Outstanding Talent Award, Taiwan
2018	Excellence in Teaching Award, Nation Taiwan University
2022-2025	Excellent Performance, National Taiwan University
2022-2025	Excellent Young Researcher Award Grant, National Science and Technology Council
2023-2026	Academic Advancement Youth Chair Professorship (學術勵進青年講座), National Taiwan University
2024	Wu Ho-Su Medical Award (吳火獅醫學獎), Taiwan

Ubiquitin Ligase RBCK1 Deficiency Unveils Mitochondrial Pathways Linking Glycogen Metabolism to Cardiomyopathy

Liang-Yu Su[1], Tzu-Han Weng[1], Ying-Chen Chen[1], Yi-Yu Lin[1], Hsin-Yu Wang[1], Ai-Ching Chen[1], Yu-Chung Pien[1], Su-Yi Tsai[1,2,3 *]

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[2]Research Center for Developmental Biology and Regenerative Medicine, National Taiwan University, Taiwan
[3]Genome and Systems Biology Degree Program, National Taiwan University, Taiwan

Glycogen, a primary energy reserve in mammals, depends on precise regulation by metabolic enzymes. While disruptions in canonical glycogen-associated proteins are well-documented causes of glycogen storage diseases (GSDs), the impact of non-glycogen-associated proteins remains underexplored. Here, our study reveals that RBCK1, a ubiquitin ligase, plays a critical role in maintaining glycogen metabolism and cardiac function. Using human pluripotent stem cell-derived cardiomyocytes, we demonstrate that RBCK1 deficiency causes significant metabolic disturbances, including excessive polyglucosan body formation, cardiomyopathy, and calcium signaling defects. Mechanistically, RBCK1 deficiency alters mitochondrial regulation and disrupts cellular glucose partitioning, leading to aberrant glycogen accumulation. Moreover, pharmacological intervention that redirects glucose metabolism reduces polyglucosan body accumulation and improves cellular energy balance. Thus, RBCK1 deficiency results in glycogen accumulation, energy imbalance, and severe cardiac phenotypes, including dilated cardiomyopathy (DCM). These findings reveal regulatory mechanisms in glycogen metabolism beyond canonical pathways and highlight potential therapeutic targets for metabolic cardiomyopathies.

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Education

2003-2006	B.Sc., Bacteriology, University of Wisconsin-Madison, USA
2007-2012	Ph.D., Chemical Biology, The Rockefeller University, USA

Research and Professional Positions Held in Chronological Sequence

2006-2007	Genome Institute of Singapore, A*STAR, Singapore Research Officer, Infectious Disease Group
2012-2017	Science and Engineering Institutes, A*STAR, Singapore Scientist I, Metabolic Engineering Research Laboratory
2018	Science and Engineering Institutes, A*STAR, Singapore Scientist II, Metabolic Engineering Research Laboratory
2018-2024	Institute of Molecular and Genomic Medicine, NHRI, Taiwan Assistant Investigator
2024~	Institute of Molecular and Genomic Medicine, NHRI, Taiwan Associate Investigator

Research Interests

Chemical proteomics • Covalent inhibitors •Post-translational modifications • Lipids • Microbial engineering • Natural products

Major Honors and Awards

2003-2006	National Science Scholarship (B.Sc.), A*STAR, Singapore
2004	Ingersoll Prize, University of Wisconsin-Madison, USA
2006	Microbiology High Achievement Award, University of Wisconsin-Madison, USA
2006	Outstanding Senior Award, University of Wisconsin-Madison, USA
2004-2006	Dean's List, University of Wisconsin-Madison
2004-2006	Chairman's Honor List, A*STAR, Singapore
2006	Roll of Honor, A*STAR, Singapore
2007-2012	National Science Scholarship (Ph.D.), A*STAR, Singapore
2012	Keystone Symposia Travel Scholarship
2023	Outstanding Paper Award by a Young Scholar, The Society of Chinese Natural Medicine, Taiwan

From Deep Sea to Immunity: Coral-derived STING Modulators

Mingzi M. Zhang
張明姿

Institute of Genomic and Molecular Medicine, National Health Research Institutes, Taiwan

Evolutionarily optimized for interactions with biomacromolecules, natural products represent a rich and diverse source of bioactive scaffolds that continue to inspire novel therapeutic strategies and chemical synthesis methodologies. Our research leverages chemical proteomics to uncover the cellular targets and mechanisms of action of natural products to identify new modes of drug target engagement and enable the development of new therapeutics.

Among the ~900 exclusively marine briarane-type diterpenoids with diverse biological activities, excavatolide B is one of the best characterized for its anti-inflammatory properties in cellular and animal models. Using a chemoproteomic strategy, we discovered excavatolide B to be a site-selective inhibitor of Stimulator of Interferon Genes (STING), a critical “switch” in the innate immune response to cytosolic DNA. We showed that excavatolide B covalently engages a specific cysteine residue on STING via its unique epoxylactone warhead to block its palmitoylation and inhibit its activity in mammalian cells. To explore the therapeutic potential of the macrocyclic briarane scaffold, we screened ~100 synthetic excavatolide B analogs generated by late-stage modification. This led to the identification of GHN105 as an orally active inhibitor that is effective against multiple human STING variants, including the pathogenic gain-of-function N154S variant causing autoinflammatory vasculopathy. GHN105 demonstrated robust on-site STING engagement *in vivo* and reversed key pathological features in a delayed-treatment acute colitis mouse model. Synthetic briarane analogs that modulate STING stability were also identified. Together, excavatolide B and its synthetic analogs constitutes a novel structural class of covalent STING modulators that offer a foundation for future therapeutic development targeting a cornerstone of innate immunity that is implicated in cancer, autoimmunity, and chronic inflammation.

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Education

1998-2003	Ph.D., Physiology, University of Freiburg, Germany
1990-1997	M.D., Medicine, China Medical University, Taiwan

Research and Professional Positions Held in Chronological Sequence

Since Aug. 2025	Chair Professor, NYCU, Taiwan
Since Nov. 2020	Dean of the School of Life Sciences, NYCU, Taiwan
Since Nov. 2023	Director of the Life Sciences Research Promotion Center (LSRPC), National Science and Technology Council, Taiwan
Since Jan. 2023	Convener of the Morphological Medicine and Physiology Division, National Science and Technology Council, Taiwan
Since Aug. 2023	Permanent Distinguished Professor at the Institute of Neuroscience, NYCU, Taiwan
2017-2023	Distinguished Professor at the Institute of Neuroscience, NYCU, Taiwan
2017-2021	Director of the Institute of Neuroscience, NYCU, Taiwan
2015-2019	Visiting Professor at Charité – Medical University of Berlin, Germany
Since Aug. 2015	Professor at the Institute of Neuroscience, National Yang Ming University, Taiwan
2011-2015	Associate Professor at the Institute of Neuroscience, National Yang Ming University, Taiwan
2006-2011	Assistant Professor at the Institute of Neuroscience, National Yang Ming University, Taiwan
2004-2006	Postdoctoral Fellow at the Department of Molecular and Cell Biology, University of California, Berkeley, USA
2003-2004	Postdoctoral Fellow at Albert-Ludwigs-Universität Freiburg, Germany
1997-1998	Resident at the Department of Neurology, National Taiwan University Hospital, Taiwan

Research Interests

We use electrophysiology *in vivo* and *ex vivo*, optogenetic/chemogenetic tools, calcium imaging, behavioral assays, viral vector, and pharmacological strategies to investigate the healthy and diseased brain. My laboratory studies brain circuits and behavior, with a recent focus on understanding neural mechanisms of emotion and cognition in the limbic system, including the hippocampus and amygdala. Using optogenetics and chemogenetics combined with

electrophysiology and calcium imaging, we establish causal relationships between circuits and behavior. We also use optogenetics-assisted circuit mapping to uncover network organization. Our research highlights the role of GABAergic circuitry in both network and cognitive functions.

Major Honors and Awards

2024	National Science and Technology Council (NSTC) Outstanding Research Award
2024	"Integrated Biomedical and Health Technology Research Program" for 6 times
2020	Honors with Qualifications for Permanent Assessment Exemption for Teachers
2012-2019	NYMU Academic Excellence Award
2016	Ministry of Science and Technology (MOST) Outstanding Research Award
2016	German Humboldt Fellowship for Experienced Researchers
2016	"Newly Approved Integrated Research Grants in Health and Medical Sciences" for 3 times
2015	Young Scientist Award - TienTe Lee Biomedical Foundation
2015	NeuroCure Fellow of Charité – Universitätsmedizin Berlin
2012	DAAD Scholarship for the research visit at the Institute for Physiology and Pathophysiology, Ruprecht-Karls-Universität Heidelberg, Germany
1998-2003	German Academic Exchange Service (DAAD) scholarship for PhD study
2008-2025	Outstanding Educator Award, School of Medicine, NYMU & NYCU

Hippocampal Mossy Cell Circuitry and Function: Anxiogenic or Anxiolytic?

Cheng-Chang Lien
連正章

Institute of Neuroscience, National Yang Ming Chiao Tung University, Taiwan

The dentate gyrus (DG) exhibits functional heterogeneity along its dorsoventral axis, with dorsal regions implicated in spatial cognition and ventral regions in emotional regulation. In this study, we investigated the distinct roles of mossy cells (MCs) in dorsal and ventral DG by combining *in vivo* calcium imaging, optogenetics, and behavioral assays in freely moving mice. We found that ventral, but not dorsal, mossy cells were selectively activated in anxiogenic environments such as the open arms of the elevated plus maze (EPM). Ventral MC activity was dynamically modulated by spatial context, increasing in anxiogenic zones and decreasing in safe zones. Circuit mapping revealed that ventral MC activation suppressed granule cell and CA1 pyramidal neuron firing, likely via recruitment of GABAergic interneurons. Chemogenetic enhancement of ventral MC excitability reduced anxiety-like behaviors across multiple paradigms. These findings suggest that ventral mossy cells exert anxiolytic effects by modulating hippocampal output via inhibitory circuit mechanisms.

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Education

1997-2004	**M.D.** National Taiwan University College of Medicine, Taipei, Taiwan
2009-2014	**Ph.D.** Institute of Physiology, National Taiwan University College of Medicine, Taipei, Taiwan

Research and Professional Positions Held in Chronological Sequence

2004~ 2008	**Residency,** Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
2008~ 2010	**Clinical electrophysiology fellowship,** Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan.
2008~ 2010	**Electrophysiology fellowship,** Human motor control section, NINDS, NIH. Advisor: Mark Hallett M.D. (2008: intramural; 2009~2010: extramural)
2011~ 2015	**Attending Physician,** Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
2013~ 2015	**Department Chief,** Department of Neurology, National Taiwan University Hospital Yin-Lin Branch
2015~	**Attending Physician,** National Taiwan University Hospital, Taipei, Taiwan Department of Medical Research: 2015～2019, 2021~
2019~ 2022	**Assistant Professor,** Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan
2021~	**Joint Faculty,** Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan
2022~	**Associate Professor,** Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan
2024~	**Deputy Director,** Molecular Imaging Center, National Taiwan University

Research Interests

Dr. Ming-Kai Pan is an Associate Professor at the Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan. He is currently running the Cerebellar Research Center at National Taiwan University Hospital, the deputy director of the Molecular Imaging Center at National Taiwan University.

He is a movement disorder specialist with a dual focus on cerebellar motor and cognitive control and their related disorders. His work has significantly advanced our understanding of the pathophysiology of essential tremor, the most common movement disorder, and has unraveled how

the cerebellum controls the detailed motor kinematics via frequency coding, and provided a unifying theory explaining normal motor control, tremors and ataxias.

In his lab, Dr. Pan drives innovation by employing cutting-edge neural dynamic technologies, bridging clinical neurology with basic neuroscience. His expertise spans cerebellar electroencephalography with dynamic spatial mapping, intraoperative cerebellar recordings, and advanced mouse-based methodologies, including tissue clearing, optogenetics, fiber photometry, calcium imaging, optical coherence tomography, and electrophysiology.

Additionally, he has made significant contributions to bioengineering, particularly in the development of novel motion-tracking technologies and volumetric super-speed microscopy.
Dr. Pan's research has been published in leading journals, including *Nature Biomedical Engineering, Science Translational Medicine*, *Journal of Clinical Investigation*, *Bioengineering & Translational Medicine*, *Science Advances*, *Advanced Science*, *PNAS*, and *Acta Neuropathologica*, reflecting his impact on both medical and neural dynamic advancements.

Major Honors and Awards

2024	**Wu Ho-Su TBF Medical Award,** Taiwan Bio-developmental Foundation
2024	**Outstanding Research Award,** National Science and Technology Council
2024	**Medical Research Award,** The New Century Health Care Promotion Foundation
2022	**Chen-Yuan Lee Medical Memorial Award**
2022	**National Innovation Award**
2020	**Young Scholar Innovation Award,** Foundation of the Advancement of Outstanding Scholarship
2020	**Young Scholar Innovation Award,** Tien Te Lee Biomedical Foundation
2018	**Junior Faculty Award,** MDS-AOS SYNERGIES 2018
2018	**Awardee, 13 Health Tech Innovators Changing the World,** APEC ASPIRE.
2018	**Future Tech Breakthrough Award,** Future Tech 2018
2018	**Best Media Notification Award,** Future Tech 2018
2018	**Ta-You Wu Memorial Award,** Ministry of Science and Technology, Taiwan
2015	**Young Star Developmental Tract Award,** Taiwan Bio-Development Foundation

Quantitative Cerebellar Codes for Motor Kinematics: Toward Numerical Precision & Cross-Individual Uniformity

Ming-Kai Pan
潘明楷

Department and Graduate Institute of Pharmacology,
National Taiwan University College of Medicine, Taiwan

Clinically, the cerebellum is best known for its role in motor coordination, particularly in constructing the fine details of motor kinematics. However, whether the cerebellum actively participates in real-time motor control remains a topic of ongoing debate. If it does, the mechanisms by which it computes kinematic parameters are still largely unknown. In this talk, I will present evidence from both mice and humans demonstrating that the cerebellum contributes to real-time motor control by encoding motor frequencies. Specifically, the cerebellum employs population coding to compute instantaneous motor frequencies underlying kinematic output. In patients with essential tremor, excessive and entrapped cerebellar oscillations give rise to involuntary, rhythmic movements at fixed frequencies. In contrast, patients with cerebellar ataxia exhibit climbing fiber regression, leading to diminished cerebellar rhythmicity and dysrhythmic motor output. These cerebellar frequency-coding algorithms offer a unifying framework for understanding kinematic encoding in both health and disease.

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Education

1997-2004	M.D., Medicine, Kaohsiung Medical University
2011-2014	Ph.D., Neuroscience, University of Cambridge

Research and Professional Positions Held in Chronological Sequence

2006-2010	Resident, Department of Neurology, National Taiwan University Hospital, National Taiwan University
2014-2015	Postdoctoral Research Associate, Institute of Psychiatry, Psychology & Neuroscience, King's College London
2016-present	Attending Neurologist, Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung Medical University
2017-2022	Assistant Professor, Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University
2022-present	Associate Professor, Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University

Research Interests

Investigating thermosensory and thermoregulatory mechanisms, particularly those mediated by TRPM2 ion channels.

Exploring the functional roles of TRP channels, neuroimmune interactions, and the molecular underpinnings of neurodegenerative diseases.

Elucidating the molecular mechanisms underlying cognitive impairment, social dysfunction, and neuroinflammation in the context of Parkinson's disease and chronic viral hepatitis.

Major Honors and Awards

2012-2014	Raymond and Beverly Sackler studentship

TRPM2 in Thermosensation and Beyond

Chun-Hsiang Tan
譚俊祥

Graduate Institute of Clinical Medicine, College of Medicine,
Kaohsiung Medical University, Taiwan

Thermosensation and thermoregulation are fundamental physiological processes essential for organismal survival and immune function. While transient receptor potential (TRP) channels are established mediators of temperature sensing, the specific contributions of individual family members remain incompletely understood. Here, we demonstrate a critical role for TRPM2 in both thermosensation, revealed through genetic deletion studies of five thermosensitive TRP channels, and thermoregulation, utilizing conditional knockout mice. Furthermore, we present evidence linking TRPM2 to the pathogenesis of inflammation-associated neurocognitive disorders, suggesting a broader role beyond thermosensation.

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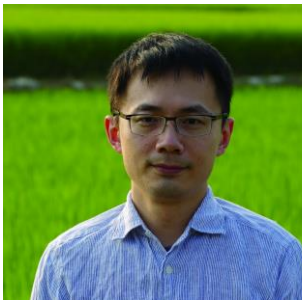


Education

2000-2005	B.S., Public Health, National Taiwan University
2005-2007	M.S., Epidemiology and Preventive Medicine, National Taiwan University
2007-2011	Ph.D., Epidemiology and Preventive Medicine, National Taiwan University

Research and Professional Positions Held in Chronological Sequence

2011-2014	Postdoctoral Scholar, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University
2014-2015	Postdoctoral Scholar, Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, U.S. Food and Drug Administration
2015-2016	Assistant Research Scholar, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University
2016-2021	Assistant Professor, College of Public Health, China Medical University
2021-2023	Associate Professor, College of Public Health, China Medical University
2023-	Associate Investigator, National Center for Geriatrics and Welfare Research, National Health Research Institutes

Research Interests

Dr. Wang has extensive research experience in genome-wide genetic data, novel genetic epidemiologic methodologies, family-based studies, and health outcome research using insurance claims databases. His research interest involves genetic architecture of brain disorders, the paternal age effect, and cognitive aging.

Major Honors and Awards

2015-2016	Scholarship for Recruitment of Science and Technology Personnel, Ministry of Science and Technology
2020	Lab member awarded with Ministry of Science and Technology College Student Research Creativity Award
2020	Award for Outstanding Research Articles of Taiwan Public Health Association
2020	Innovative Research Grant Recipient, National Health Research Institutes
2022-2025	Excellent Young Scholar Grant Recipient, National Science and Technology Council
2023-2026	Excellent Young Scholar Grant Recipient, National Science and Technology Council
2023	Ta-You Wu Memorial Award, National Science and Technology Council

Assortative Mating across Psychiatric Disorders is Consistent and Persistent over Cultures and Generations

Shi-Heng Wang
王世亨

National Center for Geriatrics and Welfare Research, National Health Research Institutes, Taiwan

Emerging evidence has shown that assortative mating (AM) is a key factor that shapes the landscape of complex human traits. It can increase the overall prevalence of disorders, influence occurrences of comorbidities, and bias estimation of genetic architectures. However, there is lack of large-scale studies to examine the cultural differences and the generational trends of AM for psychiatric disorders. Here, using national registry datasets, we conduct the largest scale of AM analyses on nine psychiatric disorders, with up to 1.4 million mated cases and 6 million matched controls. We performed meta-analyses on AM estimates from Taiwan, Denmark, and Sweden, to examine the potential impact of cultural differences. Generational changes for people born after 1930s were investigated as well. We found that AM of psychiatric disorders are consistent across nations and persistent over generations, with a small proportion of disorders showing generational changes of AM. Our results provide additional insight into the mechanisms of AM across psychiatric disorders and have evident implications on the estimation of the genetic architectures of psychiatric disorders.

Poster List

Group SRC1

Group SRC2

Group SRC3

Group SRC4

Group SRC5

Title of Project: Metabolomic Alleviation of Osteoporosis: Lipidomic Control of Epigenetic Action to Stem Cell Program

Project No.: NHRI-EX114-11029SI
P.I.: Feng-Sheng Wang/王逢興
Key Professional Personnel: Feng-Sheng Wang/王逢興, We-Shiung Lian/連韋雄, Jih-Yang Ko/郭繼陽, Ming-Hong Tai/戴明泓, Yu-Shan Chen/陳于珊, Shao-Yu Wang/王紹諭
Affiliation/Institution: Chang Gung Medical Foundation
Entire Project Period: From 2021 to 2027 (Total: 7 years)

Background: Bone tissue demonstrates osteoporosis-like features when an imbalance between osteoblastic bone formation and osteoclastic resorption develops. Epigenetic histone methylation and gut microbiota-induced dysmetabolism are involved in tissue homeostasis and remodeling. The interplay between gut microbiota-derived metabolites and histone demethylase action to bone tissue integrity remains uncharacterized

Objectives: This study aims to utilize germ-free (GF) mice, osteoblast-specific conditional H3K27me3 demethylase Utx knockout mice (UtxKO), short-chain fatty acid receptor 43 transgenic mice (Gpr43Tg) and investigate the contribution of gut microorganism-derived metabolites to bone integrity. We also investigate whether gut microbiota-derived metabolite and TCA cycle metabolite affect UtxKO and estrogen deficiency-induced osteoporosis development.

Materials and Methods: Bone mass, and key parameters of trabeculae/cortical bone network were investigated using micro-CT analysis. Gender- and age-matched GF mice were co-housed UtxKO mice. Targeted metabolome in feces and osteoblasts was characterized using ultrahigh performance liquid chromatography-tandem mass spectrometry. Methyl and acetyl histone readers were analyzed using RNA-sequencing. Wild-type mice and UtxKO mice were supplemented trimethyl-n-oxide (TMAO) and succinate in drinking water. Ex vivo osteogenic differentiation and osteogenic marker expression of bone-marrow stromal cells were evaluated using von Kossa staining and RT-PCR.

Results: UtxKO mice exhibit sex-dependent osteoporosis-like signs, including decreased bone mineral density and sparse trabeculae network and demonstrated increased levels of gut microbiota-derived lipoprotein saccharide and L-carnitine/TMAO. The dysregulated gut microbiota-derived C3-C6 fatty acid profiles correlated with impaired methyl/acetyl histone reading, and diminished mineralized matrix synthesis in UtxKO osteoblasts. Notably, transferring UtxKO gut microbiota by co-housing leads GF mice to exhibit phenotypes of low bone mass and decreased GPR43 signaling with marrow adiposity, gut inflammation and increased serum TMAO levels. Importantly, GPR43Tg mice show mitigated aging-induced severe osteoporosis. TMAO supplementation accelerates bone mass loss by activating PERK-dependent endoplasmic reticulum and mitochondrial unfolding protein response disruption to promote osteoblast senescence. Utx deletion results in cellular energetics shift between mitochondrial energy metabolism and anabolic glycolysis, particularly dysregulates hexose, AMP/GMP, and succinate/glutamate metabolism pathways. Specifically, succinate supplementation reverses Utx knockout-induced glutamate loss, ATP underproduction and osteoporosis development.

Conclusions: Our comprehensive studies convey new insight into gut-bone axis and make clear how gut microbiota-derived metabolites TMAO and short-chain fatty acids affect mitochondrial energetics/epigenetic histone actions to osteoblastic activity and bone metabolism regulated by Utx. These investigations also highlight new mitochondrial metabolite options for keeping epigenetic protection to bone tissue away from osteoporosis development.

Title of Project: Using Novel Endo-lysosomal Patch-clamp to Investigate the Mechanism of TPC2 and TRPML2 in Viral Trafficking and Its Implication in the Viral Diseases

Project No.: NHRI-EX114-11119SC
P.I.: Cheng-Chang Chen/陳政彰
Key Professional Personnel : Cheng-Chang Chen/陳政彰
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Endolysosomal ion channels are essential regulators of vesicular trafficking, membrane repair, and immune signaling. In this project, we utilize an advanced endolysosomal patch-clamp technique—developed and optimized in our laboratory—to achieve direct electrophysiological recordings from isolated intracellular organelles. This technique allows for unprecedented resolution in characterizing the functional properties of ion channels such as two-pore channel 2 (TPC2) and transient receptor potential mucolipin 2 (TRPML2), providing key insights into their roles in cellular defense mechanisms.

Our recent findings reveal that TRPML2 is selectively activated by $PI(3,5)P_2$ in $Rab4^+$ recycling endosomes, facilitating localized calcium release and vesicle trafficking toward sites of pathogen contact. TRPML2, unlike other lysosomal calcium channels, is less sensitive to $PI(4,5)P_2$, enabling its function in weakly acidic compartments. In TRPML2-knockout monocytes, we observe diminished $Rab4^+$ vesicle motility, impaired endosome recruitment, and compromised membrane repair, resulting in heightened susceptibility to microbial invasion. Notably, pharmacological activation of TRPML2 using specific small-molecule agonists restores $Rab4^+$ vesicle dynamics in deficient cells, highlighting the therapeutic potential of targeting this channel.

Beyond infection biology, this project also aims to identify novel activators and inhibitors of TPC2 and TRPML2 through high-throughput drug screening, including synthetic compounds and natural products derived from Taiwanese flora. Our work not only elucidates fundamental channel mechanisms but also demonstrates the utility of intracellular organelle electrophysiology in diverse disease contexts—including immunity, inflammation, neurodegeneration, and metabolic disorders—thereby offering new avenues for therapeutic development.

Title of Project: Investigate the Pathogenesis and Environmental Fitness of *Listeria Monocytogenes* Emerging Clone Sl87

Project No.: NHRI-EX114-11120SC
P.I.: Yu-Huan Tsai/蔡雨寰
Key Professional Personnel: You-Yan Chen/陳宥嫣, Yu-Cheng Chen/陳育丞, Dai-Ling Chang/張岱玲, Wen-Yen Weng/翁文彥
Affiliation/Institution: Chang Gung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Human listeriosis is a foodborne disease caused by *Listeria monocytogenes* (*Lm*), and presents life-threatening illness mainly characterized by bloodstream infection, maternofetal or neonatal infection, and meningoencephalitis as central nervous system infection. By collaborating with Taiwan CDC, we performed a nationwide study between 2014 and 2019 of both clinical and food *Lm* isolates and sequenced their genomes, in which in 2018 and 2019 the clinical isolates were collected in a mandatory manner in Taiwan. We found that SL87 (37.1%), SL5 and SL378 accounted for the majority (65%) of clinical cases. Unexpectedly, SL87 and SL378 were also predominant (57%) in food products. These findings indicate that, in contrast to the *Lm* in France, the *Lm* clones in Taiwan may possess both pathogenic potency and environmental persistence. In this study, we aim to study environmental persistence and pathogenicity of the major SLs prevalent in Taiwan, focusing on SL87 due to its high prevalence in clinical infection. Using human monocytic cell infection platform, we found that SL87 has the highest intracellular bacterial load among the SLs irrespective of the isolation source. Comparative genomics identified the presence of LIPI-4, a pathogenic island contributes to *Lm* invasion into central nervous system and placenta in SL4, in all the SL87 isolates but not in other isolates in Taiwan. We found that LIPI-4 expression is increased at stationary phase in BHI, suggesting that expression of LIPI-4 may be modulated by nutrient availability. We established a platform to efficiently knock out genes in SL87 without leaving any selection marker. Unexpectedly, deletion of LIPI-4 in SL87 increased intracellular survival of *Lm* in human monocytic cells. Future work will focus on the impact of the dysregulated intracellular growth in mouse model to address the implication of T cell mediated killing of infected monocytic cells. The molecular mechanism underlying LIPI-4-mediated intracellular growth control in SL87 will also be studied.

Title of Project: Analysis of Mitochondria and Nucleus Communication in Retrograde Signaling in Cardiac Cells

Project No.: NHRI-EX114-11121SC
P.I.: An-Chi Wei/魏安祺
Key Professional Personnel: An-Chi Wei/魏安祺, Yi-Ju Lee/李羿儒
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Mitochondria-to-nucleus retrograde signaling plays a pivotal role in cellular adaptation to mitochondrial dysfunction. In this study, we investigated the temporal and mechanistic landscape of retrograde communication triggered by doxorubicin (DOX), a widely used chemotherapeutic agent known to cause dose-dependent cardiotoxicity. Using a multi-omics approach, we profiled transcriptomic and metabolomic changes in human cardiomyocyte AC16 cells. Low-dose, long-term DOX treatment induced significant mitochondrial stress, characterized by elevated ROS levels, altered mitochondrial morphology, increased mtDNA copy number, and metabolic reprogramming toward glycolysis and the pentose phosphate pathway. These changes were accompanied by cellular hypertrophy, validated in human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and rat H9C2 cells. The computational analysis revealed activation of mitochondrial retrograde signaling pathways, notably involving calcium, ROS, and TCA cycle intermediates, which collectively drove transcriptional reprogramming via NF-κB, p53, and TGF-β pathways. Our results suggest that retrograde signaling not only mediates early stress adaptation, but also contributes to the progression of DOX-induced cardiac hypertrophy. The results highlight potential targets within the retrograde signaling axis for mitigating chemotherapy-induced cardiotoxicity.

Title of Project: Targeting the Ketogenesis Pathway for Tissue Rejuvenation
Project No.: NHRI-EX114-11203SI
P.I.: Patrick Ching-Ho Hsieh/謝清河
Key Professional Personnel: Yi-Chan Lee/李亦展
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2023 to 2027 (Total: 5 years)

Introduction Cardiovascular disease (CVD) poses an increasing risk to the global aging population. The interaction between aging and metabolism has emerged as a prominent area of research in understanding CVD. Previous studies have emphasized the advantageous effects of ketogenesis and its derivative β-hydroxybutyrate (β-OHB) on the heart, particularly in response to acute cardiac injury. Our previous work has elucidated that intrinsic cardiac ketogenesis promotes cardiomyocyte proliferation and enhances post-injury cardiac function through metabolic remodeling (Cheng et al., Circulation, 2022). Additionally, another study highlighted the protective role of β-OHB in reducing infarct size and preserving cardiac function during myocardial infarction (Chen et al., Nature Communications, 2023). In this study, we aim to further investigate the long-term impact of cardiac ketogenesis in the context of aging.

Hypothesis We hypothesize that cardiac ketogenesis plays a crucial role in maintaining cardiac function during the aging process.

Methods and Results To explore the impact of cardiac ketogenesis, we examined the expression of 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), a key enzyme in ketone body synthesis, in liver and heart tissues. Intriguingly, we observed age-related changes in HMGCS2 expression; while liver expression decreased, compensatory upregulation occurred in the heart. Despite this compensatory response, β-OHB levels declined in the aging heart. To further investigate the role of endogenous cardiac ketogenesis, we utilized the α-myosin heavy chain promoter-driven CRE system to specifically knockout HMGCS2 in cardiomyocytes (CM-HMGCS2$^{-/-}$). This genetic manipulation resulted in a progeroid phenotype characterized by reduced lifespan, impaired cardiac function, fibrosis, and hypertrophy in an age-dependent manner. Metabolic and mitochondrial assessments further revealed impaired mitochondrial structure in TEM analysis. Additionally, mitochondrial function assessed through Seahorse and ^{13}C-labeled metabolite consumption analysis showed a reduced oxygen consumption capability in CM-HMGCS2-/- mice.

Conclusion Our findings emphasize the critical role of endogenous cardiac ketogenesis in preserving cardiac function during aging, highlighting its potential as a therapeutic target for age-related cardiac dysfunction.

Title of Project: Modeling Rare Cardiac Disease of Polyglucosan Body Myopathy1 and Exploring Its Underlying Molecular Mechanisms

Project No.: NHRI-EX114-11232SI
P.I.: Su-Yi Tsai/蔡素宜
Key Professional Personnel: Su-Yi Tsai/蔡素宜
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Glycogen serves as a critical energy reservoir in mammals and is regulated by a range of metabolic enzymes. Mutations in these enzymes can lead to glycogen storage diseases (GSDs). Notably, polyglucosan body myopathy 1 (PGBM1), a rare GSD, results from deficiency of a non-glycogen-associated regulatory protein, leading to abnormal glycogen accumulation, early-onset muscle weakness, and dilated cardiomyopathy (DCM). However, the mechanism by which this deficiency disrupts glycogen metabolism remains poorly understood.

In this study, we employed human pluripotent stem cell-derived cardiomyocytes to model key features of the disease, including glycogen accumulation and cardiomyopathic phenotypes. We found that deficiency of this regulatory protein reduced the expression of a mitochondrial-associated factor, which in turn altered the subcellular localization of a key glycolytic enzyme. This mislocalization favored glycogen synthesis and contributed to pathological polyglucosan accumulation. Importantly, treatment with a small molecule that enhances mitochondrial enzyme activity significantly reduced glycogen accumulation.

Our findings uncover a previously unrecognized regulatory mechanism in glycogen metabolism that operates beyond canonical enzymatic pathways and suggest new avenues for therapeutic intervention in PGBM1.

Title of Project: Imbalanced Gut-lung Axis in Developing Susceptibility to Nontuberculous Mycobacterial Lung Disease: Focusing on the Immune Mechanisms and the Effect of Restoration in Gut Microbiota

Project No.: NHRI-EX114-11233SI
P.I.: Chin-Chung Shu/樹金忠
Key Professional Personnel: Hsin-Chih Lai/賴信志, Sheng-Wei Pan/潘聖衛, Shih-Hsin Wu/吳世欣
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Nontuberculous mycobacterial lung disease (NTM-LD) is increasingly recognized as a challenging condition with rising incidence, high mortality, and limited treatment efficacy. Emerging evidence suggests that host immune susceptibility, beyond microbial exposure, plays a critical role in disease development. In particular, dysfunction in macrophage and T-cell immunity has been observed in patients with NTM-LD. Our previous findings demonstrated significant gut dysbiosis, especially deficiency of *Prevotella* species, in NTM-LD patients and its association with reduced TLR2 signaling and disease severity.

In this study, we explored the immunomodulatory effects of *Prevotella* species and its capsular polysaccharides (CPS) using an antibiotic-induced dysbiosis mouse model infected with Mycobacterium *kansasii* or M. avium. Oral supplementation with either whole *Prevotella* or purified CPS reduced lung bacterial burden and reversed the dysbiosis-induced susceptibility to NTM-LD. TLR2 inhibition or knockout abrogated the protective effect of CPS but not of whole bacteria, suggesting additional mechanisms beyond TLR2. Immunophenotyping revealed increased $CD11c^+$ dendritic cells and macrophages in colon, blood, and lung, along with upregulated TLR2 and CLEC4E expression.

In vitro, *Prevotella*, its CPS or exosome protected THP-1 macrophages from NTM infection-induced cell death and reduced intracellular mycobacterial burden. Clinically, *Prevotella* abundance correlated inversely with NTM disease severity and cavitary progression. Additionally, metabolomic profiling identified altered levels of gut-derived metabolites such as allocholic acid and melatonin, which may influence immune signaling and PD-L1 expression. Exosomal PD-L1 levels in plasma and lung increased with MAC infection duration and contributed to lymphocyte apoptosis, partially reversible with PD-1/PD-L1 blockade.

In conclusion, *Prevotella* supplementation modulates the gut-lung axis through TLR2- and CLEC4E-associated pathways, restoring immune cell populations and reducing NTM susceptibility. The findings support a multifaceted mechanism involving bacterial components, immune receptors, and possibly microbiota-derived exosomes or metabolites.

Title of Project: Investigating the Mechanism of the Loss of NLRP12 Expression in Affecting Net Mediated-kidney Damage Through Ifn Signature in Lupus Nephritis Patients

Project No.: NHRI-EX114-11234SI
P.I.: Szu-Ting Chen/陳斯婷
Key Professional Personnel: Fang-Yu Tseng, Yen-Po Tsao
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Background: Systemic lupus erythematosus (SLE) is characterized by a type I interferon (IFN) signature associated with persistent autoantibodies, dysregulated immune activation, and inflammation. Nucleic acids and their corresponding antibodies form the immune complexes (NA-ICs), which contribute to disease pathogenesis. Still, their direct role in triggering the type I IFN response in neutrophils and inducing neutrophil extracellular traps (NETs) remains unclear.

Methods: Primary neutrophils were stimulated with the dsDNA-immune complexes (dsDNA-ICs) containing sera derived from SLE patients. The route of dsDNA-ICs entering the neutrophils was examined. Expression of levels of IFN-stimulated genes (ISGs), including ISG15, induced by dsDNA-ICs was measured. The involvement of gasdermin D (GSDMD) in mitochondrial pathophysiological changes and NETs formation was examined. The effect of the GSDMD inhibitor, disulfiram (DSF), for securing the mitochondrial membrane potential and preventing mtDNA cytosolic leakage was tested. In the lupus model, 28-week-old lupus-prone (B6.*Fas*^{lpr}) mice were injected with pristane and type I IFN signature, neutrophil infiltration, NET formation, and IgG deposition in the glomeruli. The effect of disulfiram treatment on IFN signature and disease progression was evaluated.

Results: In this study, pooled serum from SLE patients with high levels of anti-dsDNA antibodies induced ISG15 expression in neutrophils via Fcγ receptor-mediated endocytosis and cGAS-STING pathway activation. dsDNA-ICs containing serum stimulation activate the Caspase-4-GSDMD axis, promoting N-GSDMD mitochondria outer membrane targeting, which leads to mitochondrial depolarization and release of mitochondrial DNA into the cytosol. The cytosolic mtDNA was subsequently extruded with the expelled DNA and granule proteins, a.k.a. NET products, which further trigger type I IFN production in neutrophils. In the lupus mouse model, excessive NET formation was observed, associated with the appearance of type I IFN signature, inflammatory markers, and podocyte loss, which were ameliorated after DSF treatment. The signal intensity of ISG15 and IL-17 in the kidney of lupus-prone mice was profoundly reduced after DSF treatment, with subsequent improvement in proteinuria and glomerular inflammation.

Conclusion: These findings highlight the crucial role of nucleic acid–containing dsDNA autoantibody immune complexes in triggering the IFN-I production and activating the CASPASE4-GSDMD axis, which disrupts mitochondrial homeostasis. The tight association between interferon signature, neutrophil activation, and the progression of lupus nephritis was evidenced in the mouse model.

Title of Project: Molecular Studies of the Myocardial Ischemia-associated Type I Interferon Induction

Project No.: NHRI-EX114-11235SI
P.I.: Helene Minyi Liu/劉旻禕
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Hypoxia-Induced cGAMP Release from Cardiomyocytes Activates Macrophage STING and Exacerbates Myocardial Injury via Type I IFN Signaling

Myocardial infarction (MI) leads to ischemic injury and cardiomyocyte death, triggering innate immune responses that can exacerbate tissue damage. We investigated how hypoxic cardiomyocytes signal to macrophages and contribute to pathological inflammation via the type I interferon (IFN) axis.

Using an *in vitro* hypoxia model, we cultured HL-1 cardiomyocytes in a hypoxia chamber and collected the hypoxia-conditioned medium (HCM). HCM induced robust IFNB1 expression in RAW264.7 macrophages. The active DAMPs in HCM were heat-stable and <3 kDa, suggestive of small molecular mediators. ELISA confirmed high levels of 2’3’-cyclic GMP–AMP (cGAMP) in HCM. Pharmacological inhibition revealed that while blocking STING with H-151 abrogated IFN responses, cGAS inhibition with RU.521 had no effect, suggesting direct activation of macrophage STING by cardiomyocyte-derived cGAMP.

In a hypoxia co-culture model, HL-1 cells exhibited elevated IFNB1 expression and increased pro-apoptotic markers when cultured with RAW264.7 cells or immortalized bone marrow–derived macrophages (iBMs), but not with TNFα/TBK1-deficient iBMs. Notably, neutralization of type I IFN signaling with an anti-IFNAR antibody significantly reduced cardiomyocyte apoptosis. *In vivo*, macrophage depletion in a murine MI model attenuated cardiac injury, supporting a pathogenic role for macrophage-derived IFN.

These results support a novel model in which hypoxic cardiomyocytes release cGAMP to activate STING in macrophages, triggering a type I IFN response that amplifies myocardial injury. Ongoing studies using cell-type–specific cGAS and STING knockout mice aim to confirm the directional signaling from cardiomyocytes to macrophages via the cGAS–cGAMP–STING pathway. Our findings also suggest that anti-IFNAR therapies, such as anifrolumab, may hold therapeutic potential for MI.

NHRI-EX112-11235SI, NHRI-EX113-11235SI and NHRI-EX114-11235SI

Title of Project: Structure-based Drug Design for CFTR Chloride Channel
Project No.: NHRI-EX114-11236SI
P.I.: Tzyh-Chang Hwang/黃自強
Key Professional Personnel: Tzyh-Chang Hwang/黃自強
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Two Distinct Mechanisms for GlyH-101 block of the CFTR Chloride Channel

GlyH-101 is a commonly used pore blocker of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) to confirm the functional role of CFTR in model systems. Unlike most other anionic CFTR blockers, GlyH-101 blocks CFTR from the extracellular side, albeit previous studies suggesting an additional internal binding site. To explore the detailed mechanism of GlyH-101 block, we first examined GlyH-101's effects on a hydrolysis-deficient CFTR mutant (E1371S) whose open probability approaches unity. Whole-cell recordings with extracellularly-applied GlyH-101 revealed two phases of current reduction: a rapid initial drop within seconds and a slower decay over tens of seconds. The fast phase blockade exhibited voltage-dependent ($z\delta$ = 0.36), consistent with previously reported external pore blocking. Single-channel recordings in excised inside-out patches with GlyH-101 in the pipette solution showed a similar voltage-dependent blockade ($z\delta$ = 0.38). However, intracellular application of GlyH-101 also induced a voltage-dependent block, suggesting membrane permeation and subsequent development of external block. To decrease the membrane permeability of GlyH-101, we synthesized a hydrophilic analogue, GlyH-101-1. Application of GlyH-101-1 from cytoplasmic side of the membrane induced voltage-independent CFTR current inhibition. Single-channel recordings revealed two distinct shut states in the presence of cytoplasmic GlyH-101-1, consistent with the two-step blocking kinetics previously described for CFTRinh-172. Single-channel kinetics with a hydrophilic CFTRinh-172 analogue further confirmed this inhibitory mechanism. Taken together, our findings establish two distinct inhibitory mechanisms for GlyH-101: a voltage-dependent, on-off block through the external entrance and a two-step, voltage-independent inhibition through the internal entrance.

Title of Project: Characterize Novel Regulators of Heart– Regeneration Revealed by Comparative Time-ordered Gene Coexpression Network (TO-GCN)

Project No.: NHRI-EX114-11237SI

P.I.: Shih-Lei (Ben) Lai/賴時磊

Key Professional Personnel: Wei-Han Lang/郎偉涵, Yu-Jen Hung/洪鈺荏, Chia-Lin Huang/黃嘉琳

Affiliation/Institution: Academia Sinica

Entire Project Period: From 2023 to 2025 (Total: 3 years)

Myocardial infarction (MI) in humans causes irreversible loss of cardiomyocytes (CMs) and adverse tissue remodeling, often progressing to heart failure and death. In contrast to mammals, certain vertebrates such as zebrafish (Danio rerio) exhibit a remarkable capacity for heart regeneration. Notably, pre-depletion of cardiac-resident macrophages using clodronate liposomes (CL) significantly impairs CM proliferation and abolishes regenerative capacity, indicating that macrophages provide essential cues for CM cell-cycle reentry. However, the molecular mechanisms connecting immune activation to CM proliferation remain poorly understood.

To investigate the regulatory mechanisms underlying this immune–cardiac interaction, we performed single-nucleus ATAC sequencing (snATAC-seq) on zebrafish cardiac cells before and after injury, with and without macrophage depletion. Clustering and gene score analyses revealed a regenerative CM subset, C6, which markedly increased in proportion after cryoinjury and was enriched for dedifferentiation markers nppa and nppb. Motif enrichment analysis identified Nuclear Factor I C (Nfic) as a key transcription factor selectively activated in C6 under regenerative conditions (PBS control), but not in macrophage-depleted hearts. Correspondingly, Nfic is also identified when comparing cardiac repair in regenerative zebrafish and non-regenerative medaka using a comparative time-ordered gene coexpression network (TO-GCN) analysis. Functionally, *nfic* was reactivated in dedifferentiated CMs located at the injury border zone following injury, while *nfic* mutants exhibited impaired CM proliferation after cardiac injury, resulting in persistent fibrotic scarring compared to wild-type siblings. Mechanistically, we found that Nfic regulates the reactivation of cardiac progenitor genes critical for CM dedifferentiation, a prerequisite step for proliferation and replacing scar tissue during heart regeneration. Even in neonatal mouse CM (P1CM), knockdown of *Nfic* impaired cell proliferation, suggesting an evolutionarily conserved role of Nfic in regulating CM cycling.

Together, our findings revealed how macrophage-mediated immune activation promotes CM replenishment and identified Nfic as a key mediator of immune–cardiac crosstalk in zebrafish heart regeneration. (The project and the conference travel were generously supported by the National Health Research Institute in Taiwan/NHRI-EX114-11237SI).

Title of Project: Engineering of Therapeutic Cystine-knot Dimeric Proteins into Long-acting Single-chain Molecules

Project No.: NHRI-EX114-11238SI
P.I.: Ching-Wei Luo/羅清維
Key Professional Personnel: Ying-Wen Wang/王盈文, Chi-Ying Chen/陳祈瑩, Ching-Wei Luo/羅清維
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Cystine-knot proteins comprise many hormones and cytokines involved in metabolic diseases, aging and cancers of humans. Although being spotlighted as therapeutic proteins, challenges such as short physiological half-life and low efficiency in dimerization need to be overcome when engineering cystine-knot proteins to become protein drugs. We here proposed a new strategy that uses the C-terminal peptide (CTP), which is naturally derived from human chorionic gonadotropin and is capable of extending protein's half-life, to link two cystine-knot protein monomers. Vascular endothelial growth factor A-165 ($VEGF_{165}$), known to be critical for wound healing, was first selected as a target to demonstrate the feasibility of this design. We demonstrated that recombinant single-chain $VEGF_{165}$ (V165-CTP-V165) protein exhibited comparable bioactivities to native human VEGF165 (rhVEGF) in promoting endothelial cell proliferation, migration, and tube formation *in vitro*, and neovascularization *in vivo*. Notably, CTP modification significantly extended the VEGF's half-life in circulating blood by up to 4.5-fold and in wound exudates by up to 6-fold. When applied to a murine excisional wound model, a single topical administration of V165-CTP-V165 was sufficient to accelerate wound closure compared to rhVEGF as evidenced by enhanced neovascularization, re-epithelialization and dermal reconstitution. These findings highlight the potential of V165-CTP-V165 as an improved VEGF-based therapeutic biomaterial with enhanced stability and physiological efficacy for diverse applications, including wound care and tissue regeneration.

Title of Project: Cardiac Ageing: Development of Novel Therapeutics for Age-related Heart Failure Using Cisd2 As a Molecular Target
Project No.: NHRI-EX114-11239SI
P.I.: Chi-Hsiao Yeh/葉集孝
NHRI Researcher: Jinq-Chyi Lee/李靜琪
Key Professional Personnel : Ting-Fen Tsai/蔡亭芬
Affiliation/Institution: Chang Gung Medical Foundation
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Cardiovascular disease remains the leading cause of mortality globally, and with an aging population, the burden of age-related heart failure is rising rapidly. Despite advances in cardiovascular medicine, therapeutic strategies specifically targeting aging-associated cardiac dysfunction are limited. Our project focuses on the Cisd2 gene, a critical regulator of mitochondrial integrity, calcium homeostasis, and oxidative stress, with the aim of establishing Cisd2 as a novel therapeutic target for both age-related and hypertensive heart disease.

We hypothesize that Cisd2 plays a protective role against cardiac aging and ischemic stress by modulating mitochondrial bioenergetics and the unfolded protein response. To test this, we employed genetic mouse models including cardiac-specific Cisd2 knockout (cKO) and Cisd2 transgenic (overexpressing) lines, in combination with aging, myocardial infarction (AMI), and hypertension models. Cisd2 expression was further manipulated using three small-molecule activators, namely hesperetin, CD01, and CI58, with treatment initiated in aged mice (24–28 months) or those subjected to Angiotensin II + 1% NaCl-induced hypertension.

Our results demonstrate that Cisd2 deficiency leads to significantly increased mortality, impaired left ventricular function, and exacerbated cardiac remodeling following AMI or hypertensive stress. Echocardiography, electrocardiography, and histological staining revealed worsened ejection fraction, prolonged QTc and PR intervals, and larger cardiomyocyte cross-sectional areas in Cisd2-deficient mice. In contrast, Cisd2 overexpression or pharmacological activation preserved cardiac function, reduced myocardial fibrosis, and improved survival. These effects were reproducibly observed in both male and female cohorts.

Mechanistic studies identified eIF2α phosphorylation as a key downstream effector. Western blotting revealed that Cisd2 overexpression or activation suppressed stress-induced eIF2α phosphorylation, attenuated endoplasmic reticulum stress, and preserved calcium balance. These pathways collectively supported mitochondrial function and mitigated reactive oxygen species accumulation during cardiac stress. CD01 and CI58 treatments notably improved systolic blood pressure and cardiomyocyte morphology in hypertensive aged mice.

Furthermore, we conducted transcriptomic profiling of heart tissue at early stages post-AMI, identifying gene expression signatures linked to inflammation, apoptosis, and translational regulation. Gene ontology and pathway analyses corroborated the role of Cisd2 in modulating cellular stress responses and protein synthesis machinery. Notably, survival analysis in hypertensive mice showed that both CD01 and CI58 significantly extended survival, even in Cisd2-deficient settings, suggesting additional compensatory mechanisms worth future exploration.

In conclusion, our findings provide strong preclinical evidence that enhancing Cisd2 activity, either genetically or pharmacologically, represents a promising therapeutic strategy for combating age-related and hypertension-induced cardiac dysfunction. Targeting the Cisd2-eIF2α-ER stress axis offers a mechanistically grounded approach to preserve cardiac health in the elderly, with potential clinical applications for preventing or delaying the onset of heart failure.

Title of Project: Study the Physiological Function of the Miltenberger Blood Group Antigen Type III (GP.Mur) and Explore Its Gene Evolution in Taiwan.

Project No.: NHRI-EX114-11313SI

P.I.: Yei-Tsung Chen/陳儀聰

Key Professional Personnel: Ferry Saputra, Wen-Ya Ko, Yei-Tsung Chen

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

The Miltenberger (Mi) blood group system comprises a group of phenotypically related red blood cell antigens that arise from hybrid glycophorin proteins (GPs), primarily due to gene recombination involving *GYPA* and *GYPB*. Among these, glycophorin Mur (GP.Mur, aka Mi.III) is the most clinically significant and frequently encountered variant, which is prevalent in Southeast Asia nations, including Taiwan. The prevalence of GP.Mur in Taiwan is around 4.5 %, with a higher prevalence found in the population residing in eastern Taiwan, especially within the indigenous populations. Prior genetic studies have revealed that GP.Mur results from a specific hybrid glycophorin gene that encodes a protein combining sequences from glycophorin A and B, and creating a unique membrane epitope. Further biochemical studies suggest the hybrid glycophorin in the red blood cell may contribute to the superior physical endurance of the individuals who bear this blood type. It becomes apparent that the functional integrity of red blood cells is essential for the homeostasis of the cardiovascular system, and GPs have been known to play roles in the architecture of red cell membranes; nevertheless, the underlying mechanism concerning GPs has yet to be defined. In this study, we aim to investigate the correlation of GPA, GPB, and GP.Mur with cardiac function, as well as the appearance of GPs in metabolomic and transcriptomic landscapes. For this purpose, the zebrafish has been chosen to create the animal model for study, not only due to its genetic and physiological homology with humans, but more importantly, zebrafish contain only the GPC orthologs but not GPA, GPB, and GP.Mur. Thus, the result from the zebrafish model might reflect the biological function of GPs without the disturbance from orthologous genes. To date, humanized zebrafish lines bearing human GPs (hGypA, hGypB, and hGypB-A-B) have been created. The success of the gene transduction of the human glycophorins was evidenced by the appearance of fluorescent flag in the zebrafish larvae 3 days post-microinjection. The gross morphology and mobility of transgenic zebrafishes are comparable to AB line zebrafish at different stages, suggesting that the appearance of human GPs in zebrafish might not affect the development of zebrafish and be functionally tolerable across species. Currently, we are in the middle of assessing the effect of human GPs on cardiac function in larvae; subsequent detailed morphological and histological analyses, as well as the susceptibility test of the humanized zebrafish upon hypoxic and excessive adrenergic activation will be examined to delineate the plausible involvement of GPs in the pathogenesis of cardiovascular diseases.

Title of Project: Exploring the Role of Aerobic Glycolysis in the Development of Sinus Node Dysfunction

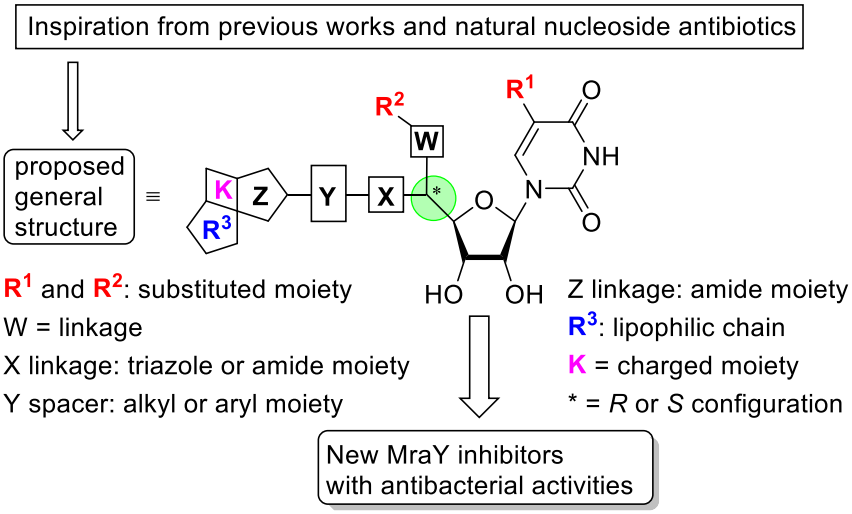
Project No.: NHRI-EX114-11314SI
P.I.: Yu Feng Hu/胡瑜峰
Key Professional Personnel: Yu-Cheng Su, Mu Jou Tseng, Pei-Chun Chou, Chih-Min Liu, Ching-Hui Weng, Peng-Chin Tsai
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Sinoatrial node dysfunction (SND), the leading cause of rhythmic failure, currently lacks diverse treatment options beyond implanted electronic pacemakers. This research hypothesizes Aldolase C (Aldoc) deficiency as a novel pathogenic mechanism for SND, aiming to develop a targeted metabolic therapy. Initial studies in aging mice, exhibiting SND symptoms like bradycardia and exercise intolerance, revealed reduced heart rate and impaired sinoatrial node (SAN) function. Proteomic analysis of their SAN tissue indicated dysregulation in energy utilization pathways, particularly glycolysis, with a significant reduction in Aldoc. This link was strengthened by observing heart rate suppression in mice after glycolysis inhibition. The Aldoc supplement reversed cardiac pause in aging mice. Further investigation using heterozygous Aldoc knockout zebrafish demonstrated lower heart rates and reduced exercise capacity, underscoring Aldoc's crucial role in SAN rhythm and activity. The inability of homozygous Aldoc knockout fish to survive the embryonic stage highlights Aldoc's vital function in development. The research plans to perform single-cell sequencing to understand transcriptome changes in pacemaker cells. A conditional cardiac-specific Aldoc knockout mouse model has been developed and will precisely pinpoint the gene-disease causality. The ultimate goal is to pioneer device-free metabolic treatments for SND by activating Aldoc and restoring glycolysis, potentially even enabling primary prevention of the condition.

Title of Project: Discovery of Novel Nucleoside-based Mray Inhibitors to Block Bacterial Peptidoglycan Cell Wall Assembly: from Complex Natural Products to Potential Antibiotic Development

Project No.: NHRI-EX114-11315SI
P.I.: Wei-Chieh Cheng/鄭偉杰
Key Professional Personnel: Chun-Kai Wang/王鈞楷, Shih-Chen Ho/何師辰
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Inspired by the uridine-containing natural products, a progressive synthetic method toward 5'-substituted uridine-based inhibitors against MraY, the essential enzyme for bacterial PGN synthesis, was established. We systematically prepared a series of molecules with an 5'-aminoribosyl uridine moiety with modifications of the configuration at 5'-position, lipophilic group, appendant charged group, spacer, and linkage type; and then screened via HPLC-based functional assay. The pentadecanoic (C15) substituted 5'-(S)-aminoribosyl-triazolyl uridines with positively charged (NH3+) moiety (compounds 19 and 20) were demonstrated to be effective MraY inhibitors. In the enzymatic inhibition assay, hit compound 19 (IC50 = 2.2 μM) showed a 10-fold improvement compared to Tunicamycin (IC50 = 30 μM), the well-known MraY inhibitor. Besides, compound 19 exhibited potent antibacterial activities against Gram-positive and resistant bacteria.



Title of Project: Investigating the Reno-protective Effect of Tamoxifen on Ischemia-reperfusion Injury Through Regulation of Amino Acid Transporter and Lipid Accumulation- Focusing on Renal Tubular Cells and Pericytes

Project No.: NHRI-EX114-11316SC
P.I.: Yu-Hsiang Chou/周鈺翔
Key Professional Personnel: Yu-Han Shao/邵鈺涵, Hui-Chiun Tseng/曾惠群
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Background Acute kidney injury (AKI) is associated with various complications, including an increased risk of developing chronic kidney disease (CKD). Elucidating the underlying mechanisms of AKI is essential for the development of effective therapeutic strategies. Metabolic alterations following AKI may contribute to the progression of CKD. We previously demonstrated that pretreatment with tamoxifen (TAM) attenuates the severity of ischemia-reperfusion injury (IRI)-induced AKI. Based on this, we hypothesized that TAM-induced changes in amino acid and lipid metabolism may promote renal recovery after IRI-AKI.

Methods To investigate the effects of TAM in AKI, we employed the translating ribosome affinity purification (TRAP) technique in *Pax8-rtTA;LC-1;EGFP-L10a* triple-transgenic mice to isolate and sequence mRNA specifically from renal tubular cells following IRI-induced AKI. Mice pretreated with TAM were subjected to single-nucleus RNA sequencing (snRNA-seq) and analysis of amino acid levels in plasma, kidney tissue, and urine. Amino acid quantification was performed using a custom-developed liquid chromatography–mass spectrometry (LC-MS) platform. Additionally, to explore metabolic changes in pericytes post-injury, we used 3T3 fibroblast cells stimulated with TGF-β1 to simulate the activated pericyte phenotype following AKI.

Results We found that expression levels of amino acid transporters, including *Slc7a12* and *Slc3a2*, were significantly elevated in TAM-treated mice compared to controls. Gene set enrichment analysis (GSEA) confirmed the upregulation of pathways related to amino acid transport in the TAM group. snRNA-seq further revealed a marked increase in *Slc7a12* expression in the S3 segment of proximal tubular cells following TAM administration. To functionally validate these findings, we generated *Slc7a12* knockout mice using CRISPR/Cas9 technology. TAM pretreatment led to reduced levels of leucine in plasma and urine of the mice following IRI-AKI, indicating decreased urinary leucine loss and enhanced renal retention of leucine. In addition, the expression of lipid metabolism-associated genes *Ugt1a2* and *PXR* was upregulated in renal tubular cells of TAM-treated mice after IRI-AKI. *In vitro* studies showed that the expression of mitochondria-associated protein *Slc25a12* was reduced in 3T3 cells after TGF-β1 stimulation, suggesting potential involvement in pericyte metabolic regulation.

Conclusions Alterations in amino acid and lipid metabolism appear to play a critical role in the recovery process following IRI-induced AKI. The upregulation of Slc7a12, an amino acid transporter, and Ugt1a2, a lipid metabolism-related protein, in renal tubular cells of TAM-treated mice may underlie the reno-protective effects observed with TAM pretreatment. Future studies will employ renal tubular cell-specific *Slc7a12* and *Ugt1a2* knockout models to further elucidate their functional roles in AKI. Additionally, the role of the mitochondrial protein Slc25a12 in pericyte responses during AKI will also be investigated.

Title of Project: The Functional Role of a Novel E3 Ubiquitin Ligase in the Regulation of Necroptosis
Project No.: NHRI-EX114-11334SI
P.I.: Li-Chung Hsu/徐立中
Key Professional Personnel: Tzu-Yu Pu/蒲姿佑, Hsien-Ping Chiu/邱顯平, You-Sheng Lin/林祐聖, Gina Chen/陳可馨
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Necroptosis is a lytic, caspase-independent form of programmed cell death induced by various stimuli that activate pattern recognition receptors (PRRs) or death receptors (DRs). Upon activation, receptor-interacting serine/threonine-protein kinase 3 (RIPK3) becomes activated and subsequently phosphorylates mixed lineage kinase domain-like pseudokinase (MLKL), which triggers necrotic cell death. Numerous studies have demonstrated that necroptosis plays critical roles in a range of physiological processes, including host defense against pathogens and tumors, as well as in development and tissue regeneration. However, uncontrolled necroptosis is detrimental and has been implicated in inflammatory diseases. Our laboratory previously identified a novel E3 ubiquitin ligase as a key modulator of Toll-like receptor (TLR)-mediated immune responses, demonstrating that by ubiquitinating specific protein substrates, this E3 ubiquitin ligase orchestrates distinct immune signaling pathways. To further investigate its biological functions, we conducted unbiased ubiquitylome and proteome analyses and identified RIPK3 as a novel interacting partner of this E3 ubiquitin ligase, suggesting a potential role in regulating necroptosis. In this study, we found that deletion of this E3 ubiquitin ligase in murine bone marrow-derived macrophages (BMDMs) and RAW264.7 cells suppressed cell death and reduced phosphorylation of RIPK3 and MLKL following stimulation with poly(I:C) or LPS in the presence of the pan-caspase inhibitor zVAD, indicating that this E3 ubiquitin ligase is involved in TRIF-dependent necroptosis. We further demonstrated that RIPK3 interacts with this E3 ubiquitin ligase through both its kinase domain and RIP homotypic interaction motif (RHIM). Importantly, we found that the E3 ligase activity of this protein is required to promote TRIF-dependent necroptosis and is necessary for efficient necrosome complex formation. Collectively, our findings suggest that this E3 ubiquitin ligase acts as a positive regulator of TRIF-dependent necroptosis through its E3 ligase activity.

Title of Project: To Investigate the Mechanism of PP4 in Regulating Nets Formation During Sepsis
Project No.: NHRI-EX114-11335SI
P.I.: Feng-Ming Yang/楊豐名
Key Professional Personnel: Mei-Chun Lin/林玫君, Yu-Ting Huang/黃鈺婷, Wei-Ruei Jiang/江為睿
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Background: Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated immune response to infection, remains a major cause of mortality in critical care. Acute lung injury (ALI) is one of its most severe manifestations, driven by excessive inflammatory signaling, innate immune dysregulation, and neutrophil hyperactivation. Key signaling pathways mediated by Toll-like receptor 4 (TLR4), tumor necrosis factor receptor-associated factor 6 (TRAF6), and their regulators have emerged as important targets for modulating sepsis pathology.

Objective: This study investigates how two critical regulators-cylindromatosis (CYLD) and serine/threonine protein phosphatase 4 (PP4)-modulate TLR4-mediated responses, neutrophil extracellular trap (NET) formation, and cytokine signaling during sepsis-induced ALI.

Methods and Results: Our data show that CYLD directly binds to somatic nuclear autoantigenic sperm protein (sNASP) to suppress TRAF6 activation. Upon TLR4 stimulation, sNASP phosphorylation displaces CYLD, allowing TRAF6 autoubiquitination and proinflammatory cytokine release. This activation is reversed upon sNASP dephosphorylation by PP4, reassembling the CYLD/sNASP/TRAF6 complex and suppressing inflammatory responses. Mice treated with adenovirus-expressing CYLD WT, not mutant, showed significant protection from cecal ligation and puncture (CLP)-induced lung injury and reduced cytokine production. To further define PP4's regulatory role, we generated myeloid-specific PP4 knockout (PP4 flox/flox LysM-Cre) mice. These mice were more susceptible to sepsis and exhibited elevated levels of IL-6, TNF-α, MIP-1α, and CCL5 following endotoxin exposure, along with profound tissue injury. Increased extracellular DNA and NET formation were observed in PP4-deficient mice and were positively correlated with macrophage-derived chemokine overproduction. Mechanistically, PP4 suppressed these responses via dephosphorylation of TBK1, thereby reducing IRF3-mediated CCL5 transcription, and through modulation of autophagy/LC3-associated phagocytosis (LAP) pathways, which directly control NETosis. Loss of PP4 also led to enhanced ERK1/2 activation and CCR5 expression in neutrophils, amplifying CCL5-driven NET formation and oxidative stress.

Conclusion: Our findings uncover a coordinated regulatory network wherein CYLD and PP4 dampen TLR4-triggered inflammatory signaling through distinct but complementary pathways. CYLD restrains TRAF6/sNASP axis activation**,** while PP4 modulates macrophage-neutrophil communication and NET formation via TBK1/IRF3 and LAP-dependent mechanisms. These insights suggest novel therapeutic targets for restoring immune homeostasis and mitigating lung injury in sepsis.

Title of Project: Investigating the Pathophysiological Mechanism of K2P Channelopathy in Maturity Onset Diabetes of the Young
Project No.: NHRI-EX114-11336SI
P.I.: Shi-Bing Yang/楊世斌
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Spatiotemporal Distribution of TALK1-L114P in β-Cells Links Transient Neonatal Diabetes to Maturity-Onset Diabetes of the Young (MODY)

Abstract: A gain-of-function missense mutation in the pancreas-specific potassium channel TALK1 (TALK1-L114P) has been identified as a monogenic cause of maturity-onset diabetes of the young (MODY). In a transgenic mouse model carrying this mutation, most neonatal mice develop transient severe hyperglycemia, with only a subset surviving beyond the early postnatal period. Among survivors, β-cell excitability and glucose tolerance vary markedly with age. Although TALK1-L114P enhances K^+ conductance, the mechanisms driving the age-dependent and heterogeneous diabetic phenotypes remain unclear. Here, we performed age-stratified electrophysiological analyses to investigate the molecular and physiological mechanisms of the TALK1-L114P mutation in diabetogenesis. We found TALK1 channel exhibits age-dependent trafficking regulation. In neonates, high membrane potassium conductance causes β-cell hyperpolarization, impaired insulin secretion, and hyperglycemia. In contrast, reduced membrane targeting during late postnatal development partially restores insulin secretion and alleviates the diabetic phenotype. Nevertheless, persistent heterogeneity in mutant channel expression among adult β-cells continues to affect excitability, contributing to MODY-like symptoms. Mathematical modeling supports that altered basal K^+ conductance from TALK1-L114P perturbs membrane potential and intracellular calcium dynamics. Together, these findings demonstrate a unique age-dependent trafficking of TALK1 channels and highlight the pivotal role of TALK1 in regulating β-cell membrane excitability.

Title of Project: Role of Endothelial ER Protein TXNDC5 in Pulmonary Arterial Hypertension: Mechanistical Insights into Endothelial-Mesenchymal Transition

Project No.: NHRI-EX113-11138SI
P.I.: Wei-Ting Chang/張瑋婷
Key Professional Personnel : Kai-Chien Yan/楊鎧鍵
Affiliation/Institution: Chi Mei Medical Center
Entire Project Period: From 2022 to 2024 (Total: 3 years)

Background: Endothelial to mesenchymal transition (EndMT) is implicated in pulmonary arterial hypertension (PAH) but remains poorly understood. Thioredoxin domain containing 5 (TXNDC5), an ER-resident protein, plays a role in pulmonary hypertension; however, its involvement in pulmonary artery remodeling is unclear. Hereby, we studied the regulatory mechanism of TXNDC5 by promoting EndMT in pulmonary artery remodeling and subsequent right ventricular failure.

Methods and Results: In pulmonary arterial tissues of PAH patients, TXNDC5 expression was elevated compared to control tissues. Additionally, levels of the endothelial marker VE-cadherin decreased, while markers for mesenchymal cells, such as vimentin and alpha smooth muscle actin (αSMA), along with EndMT-associated markers, increased, especially in TXNDC5-positive cells. In endothelial cell-specific reporter mice (Cdh5-Cre/ERT2; tdTomato), high TXNDC5 expression was observed in cells co-expressing Tomato and mesenchymal cell markers following Sugen/hypoxia treatment, suggesting that PAH induced TXNDC5 upregulation and EndMT. These effects were reversed in both global and endothelial-specific TXNDC5 knockout mice. Mechanistically, suppression of HIF-1 signaling reduced TXNDC5 levels, while TXNDC5 inhibition downregulated both HIF-1α and HIF-1β. Promoter assays indicated that HIF-1β (Arnt) acts as a transcription factor for TXNDC5, with downstream SMAD3 also regulating HIF-1β transcription, forming a positive feedback loop. Furthermore, targeting TXNDC5 with aptamers in PAH mouse models reduced pulmonary hypertension and improved right ventricular function.

Conclusions: PAH increases TXNDC5 production, triggering EndMT in PAH. Targeting TXNDC5 could be a promising therapeutic approach to reduce pulmonary hypertension and improve right ventricular function in PAH patients.

Keywords: TXNDC5, PAH, EndMT

Title of Project: Engineered Molecular Warheads Target Virus-Infected Mosquitoes
Project No.: NHRI-EX114-11438SI
P.I.: Ming-Jiun Yu/余明俊
Key Professional Personnel : Yu-Ning Huang/黃鈺甯
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Combat Dengue Virus Infection in the *Aedes aegypti* Mosquito Cells

Dengue virus infects between 100 and 400 million people each year, posing a significant threat to global public health. Transmission occurs when infected female mosquitoes bite humans to obtain nutrients from blood for egg development. Due to the lack of effective treatments or vaccines, recent efforts have focused on preventing virus transmission within mosquitoes. To address this, we developed VOUDOU (Virus-Operated Up- or Down-expression of yOUr gene), a synthetic gene expression system activated by viral infection. The VOUDOU construct comprises full-length NS4B, ten amino acids from NS5, and a nuclear localization signal (NLS)-tagged yeast transcription factor Gal4 (forming NS4B-NS5-NLS-Gal4), together with a gene of interest under the control of an upstream activating sequence (UAS). Before infection, the recombinant protein remains anchored to the endoplasmic reticulum membrane. When the dengue virus infects the cell, its protease NS3 cleaves the NS4B-NS5 junction, releasing NS5-NLS-Gal4. This cleaved fragment translocates to the nucleus, initiating transcription of the gene of interest. Using GFP as a reporter gene, we confirmed that virus infection triggers GFP expression. We explored two gene targets to interfere with virus transmission: Leucokinin, a diuretic peptide hormone released by female mosquitoes to eliminate the excess water from a blood meal (which can weigh twice the mosquito's body weight). VOUDOU-mediated expression of leucokinin was expected to induce excessive diuresis, leading to mosquito dehydration and death. In Aedes aegypti CCL-125 cells stably expressing the VOUDOU-leucokinin construct, dengue virus infection elevated leucokinin mRNA levels. Furthermore, conditioned medium from these infected cells enhanced fluid secretion by isolated mosquito Malpighian tubules by 1.5-fold. ATP synthase subunit β (ATPB), an essential component of mitochondrial oxidative phosphorylation, was upregulated in dengue-infected mosquitoes according to our transcriptomic analysis. RNA interference against ATPB reduced dengue virus RNA replication in mosquito bodies and midguts. To harness this, we engineered VOUDOU-miATPB, which expresses a microRNA targeting ATPB upon infection. In CCL-125 cells, dengue virus infection led to a fourfold increase in ATPB-targeting pre-miRNA levels by day 3 post-infection. This was accompanied by a reduction in ATPB mRNA and decreased viral replication. In conclusion, the VOUDOU system offers a flexible platform to combat dengue virus in mosquitoes by either inducing harmful physiological responses or suppressing host factors that support viral replication.

Title of Project: Engineered Molecular Warheads Target Virus-Infected Mosquitoes
Project No.: NHRI-EX114-11438SI
P.I.: Ming-Jiun Yu/余明俊
Key Professional Personnel : Hsin-Hsin Wu/吳欣芯
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

VOUDOU: A Virus-Activated Gene Circuit for Zika-Triggered Mosquito Self-Elimination

Zika virus (ZIKV) poses serious health risks, including microcephaly in infants and Guillain-Barré syndrome. With no approved vaccine, new control methods are needed. As ZIKV is primarily transmitted by *Aedes aegypti* mosquitoes, we propose to engineer transgenic mosquitoes carrying a virus-induced lethal gene to ensure self-elimination upon infection. To this end, we developed VOUDOU (Virus-Operated Up- or Down-expression of yOUr gene), a virus-activated synthetic gene expression system. The construct includes full-length NS4B, a ten-amino acid segment from NS5, and a Gal4 transcription factor fused with a nuclear localization signal (NLS), forming the recombinant protein NS4B-NS5-NLS-Gal4. This protein remains anchored to the endoplasmic reticulum under uninfected conditions. Upon Zika virus infection, the viral protease NS3 specifically cleaves the NS4B-NS5 junction, releasing NS5-NLS-Gal4 from the membrane. The released fragment then translocates to the nucleus, where Gal4 binds to the upstream activating sequence (UAS) and activates expression of miIAP, a microRNA targeting inhibitor of apoptosis protein 1 (IAP1). Down expression of IAP1 is anticipated to induce apoptosis in infected mosquitoes. The VOUDOU-miIAP plasmid plus a transposase plasmid were co-injected into 406 embryos, only one mosquito showed genomic insertion (transformation efficiency: 0.25%). To improve transformation efficiency, we engineered an all-in-one construct that combines both the transposase and a transposon cargo (NLS-GAL4-UAS-eGFP) flanked by the terminal repeat sequences. A total of 585 *Aedes aegypti* embryos were injected with the construct. Fifteen mosquitoes expressed eGFP, raising the transformation efficiency to 2.07%, more than 8 times higher than injecting two separate constructs at the same time. Next, we replaced NLS-GAL4-UAS-eGFP with VOUDOU-miIAP and incorporated mCherry as the selection marker. The construct was tested in *Aedes aegypti* CCL-125 cells. In the wild-type cells, ZIKV infection increased IAP mRNA expression. In the transfected cells, ZIKV infection suppressed the above increase, in line with the activity of miIAP. These findings reveal intricate virus-host interactions that might be exploited for targeted mosquito elimination and ZIKV transmission control.

Title of Project: The Role of TRPM2 in Inflammation-associated Neurocognitive Disorders
Project No.: NHRI-EX114-11115NC
P.I.: Chun-Hsiang Tan/譚俊祥
Key Professional Personnel: Chun-Hsiang Tan/譚俊祥, Rwei-Ling Yu/余睿羚, Yu-Chen Cheng/鄭郁蓁
Affiliation/Institution: Kaohsiung Medical University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Background and aim: The transient receptor potential melastatin 2 (TRPM2) ion channel has emerged as a key transducer of temperature and oxidative stress signals. Its strategic expression in neurons, microglia, and leukocytes positions it at the intersection of neuroinflammation and immune responses. Here, we hypothesize that TRPM2 serves as a central mediator driving the pathogenesis of inflammation-associated neurocognitive disorders. Our study seeks to elucidate the cell-specific roles of TRPM2 across diverse cellular populations in these conditions.

Methods: To investigate the role of TRPM2 in inflammation-associated neurocognitive disorders and evaluate the impact of sex hormones on these conditions, we conducted a comprehensive study using both global and conditional knockout (KO) mice models. Conditional KOs were generated by crossing STOCK *Trpm2*$^{tm1.1Dpc}$/J mice with Cre lines targeting cortical neurons (STOCK Tg(Actl6b-Cre)4092Jiwu/J), microglia (C57BL/6-*Tmem119*$^{em1(cre/ERT2)Gfng}$/J), and hematopoietic cells (B6.Cg-*Commd10*$^{Tg(Vav1-icre)A2Kio}$/J). Inducible deletion of TRPM2 in microglia was achieved via tamoxifen administration. Inflammation was induced using lipopolysaccharide (LPS), while sex hormone influences were evaluated by administering 4-Vinylcyclohexene dioxide (VCD) and testosterone undecanoate. We also compared the effects of TRPM2 global knockout between male and female mice. Cognitive function was assessed using the Barnes Maze test, and motor coordination was evaluated with rotarod and pole tests. Cre-driver lines were validated by crossing them with tdTomato reporter (B6.*Cg-Gt(ROSA)26Sor*$^{tm9(CAG-tdTomato)Hze}$/J) mice. STOCK *Trpm2*$^{tm1.1(icre)Jsmn}$/J mice were crossed with tdTomato reporter mice to delineate expression profiles of TRPM2.

Results: We observed significant sex-dependent differences in cognitive performance after LPS injections following global TRPM2 deletion. Male mice with global TRPM2 knockout exhibited better performance on the Barnes Maze compared to their littermates with intact TRPM2. However, this protective effect was not observed in female mice. Furthermore, female mice treated with VCD and testosterone undecanoate showed significantly worse cognitive performance. Among conditional KO mice, deletion of TRPM2 in microglia or cortical neurons resulted in better cognitive performance, while deletion in hematopoietic cells led to worse performance compared to littermate controls.

Conclusion: Our findings reveal sex-specific roles of TRPM2 in mediating inflammation-associated neurocognitive disorders. Specifically, TRPM2 expression in cortical neurons and microglia appears detrimental in inflammation-associated neurocognitive disorders, while its expression in hematopoietic cells confers protective effects. These insights underscore the complex and nuanced involvement of TRPM2 in neuroinflammation and immune responses, highlighting potential therapeutic targets for inflammation-associated neurocognitive disorders.

Title of Project: The Association Among Monocyte/macrophage of the Innate Immunity, Antipsychotics Exposure, and Vascular Atherosclerosis in Schizophrenic Disorder

Project No.: NHRI-EX114-11201NI
P.I.: Shang-Ying Tsai/蔡尚穎
Key Professional Personnel: Cheng-ying Hsieh/謝政穎, Pao-Huan Chen/陳抱寰
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2023 to 2027 (Total: 5 years)

Background and Objectives Our previous NIRH-funded study demonstrated accelerated atherosclerosis in patients with SCZ. Monocytes and monocyte-derived macrophages play central roles in the initiation and progression of atherosclerosis. Accordingly, we hypothesized that accelerated atherosclerosis is associated with specific monocyte/macrophage activation patterns in SCZ. This study aimed to examine which monocyte/macrophage phenotypes with specific surface markers and clinical features are associated with accelerated atherosclerosis.

Methods Physically healthy and clinically stable outpatients with schizophrenia (DSM-5) and normal controls (NC) aged < 60 years were recruited to undergo carotid intima-media thickness (CIMT) measurement via high-resolution ultrasonography. Participants with substance abuse, concurrent medical conditions or trauma, BMI > 30 kg/m², and pregnancy were excluded. Clinical data were obtained through medical record review and direct patient interviews. Flow cytometry characterization of circulating monocyte/macrophage lineage cells was performed using specific M1 (CD80, CD86, CD284) and M2 surface markers (CD204, CD163, CD206). Elevated CIMT was defined according to the consensus statement from the American Society of Echocardiography.

Results Patients with SCZ (N=119) demonstrated significantly higher CIMT values compared to NC (N=109) (0.57 ± 0.14 mm vs. 0.51 ± 0.08 mm, t=3.9, p<0.001). Elevated CIMT was identified in 40.3% of SCZ patients (N = 48). Compared to SCZ patients with normal CIMT, those with elevated CIMT exhibited significantly higher ratios of classical M1 monocytes CD86+ (CD14+CD16－CD86+) and M1 macrophages CD86+ (CD14+CD16 － CD11b+CD86+). No significant differences were observed in physical activity intensity, lipid profiles, BMI, antipsychotic exposure duration, medication dosage, or other clinical characteristics between the two subgroups. Logistic regression analysis identified higher ratio of classical M1 monocytes CD86+ as significant predictors of elevated CIMT.

Conclusions Given that circulating CD86+ monocytes serve as biomarkers for active vascular inflammation, this study provides the first evidence that persistent activation of classical M1 (pro-inflammatory) CD86+ monocytes in circulation, rather than medication exposure or lipid profiles, may contribute to chronic vascular inflammation and accelerated atherosclerosis in patients with SCZ.

Title of Project: Mechanistic Link from Amyloidosis to Tauopathy in Alzheimer's Disease: Role of Glutamate Transporter

Project No.: NHRI-EX114-11207NI
P.I.: Yu-Min Kuo/郭余民
Key Professional Personnel: Tzu-Feng Wang/王姿丰
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2023 to 2026 (Total: 4 years)

Amyloid and tau PET imaging, along with cerebrospinal fluid biomarker analyses, have categorized Alzheimer's disease (AD) pathology into sequential A (Aβ), T (Tau), and N (neurodegeneration) stages. Interestingly, in some individuals, disease progression appears to stall for years at the $A^+/T^-/N^-$ stage, suggesting the existence of regulatory mechanisms that modulate the transition from A^+/T^- to A^+/T^+ ($A^+/T^- \rightarrow A^+/T^+$). By analyzing glia-specific expression residuals across two independent cohorts, we identified SLC1A2 as a key regulator of AD-related genes. SLC1A2 encodes EAAT2, which, together with EAAT1, is predominantly expressed in astrocytes and is essential for clearing synaptic glutamate. We propose that EAAT1/2-mediated excitotoxicity is a critical driver of $A^+/T^- \rightarrow A^+/T^+$. Initially, we examined the effect of GLAST and GLT-1 (the mouse equivalents of EAAT1/2) knockdown on AD pathology by infusing AAVs with GFAP promoter-driven shRNAs targeting GLAST and GLT-1 into the bilateral dorsal hippocampus (dHPC) of 3xTg-AD mice (termed KD mice) at 14.5 months of age. Six weeks later (at 16 months of age), KD mice showed impaired learning and memory performance, increased local excitotoxicity, worsened Tau pathology, without affecting local Aβ pathology, especially in female 3xTg-AD mice. To test if excitotoxicity contributes to the worsened tauopathy, we induced excitotoxicity in 16-month-old female 3xTg-AD mice by injecting kainic acid (i.p.) for three days. The results showed that KA treatment significantly increased p25/p35 expression ratios and pTau levels in the dHPC without influencing amyloid plaque (AP) load, support that excitotoxicity can drive the $A^+/T^- \rightarrow A^+/T^+$ transition. Next, we overexpressed GLAST and GLT-1 in the dHPC of 3xTg-AD mice (termed OE mice), following the same timeline as the KD study. The results showed that OE mice had improved performance in learning and memory, alleviated tau pathology, but had no changes in the local levels of soluble Aβ or AP load. In 5xFAD mice, amyloidosis severity increased with age in 5xFAD mice and was more pronounced in females than in males. Female 5xFAD mice, but not males, exhibited impaired spatial learning and memory, reduced levels of GLAST and GLT-1 in the dHPC. Furthermore, GLAST and GLT-1 levels were negatively correlated with the severity of local amyloid pathology, particularly with the levels of AP load. Next, we examined riluzole (RLZ), an FDA-approved drug known to increase GLAST and GLT-1 expression on the $A^+/T^- \rightarrow A^+/T^+$ transition. Daily administration of RLZ to 15-month-old female 3xTg-AD mice for 28 d improved spatial learning and memory, increased GLAST and GLT-1 expression levels in the dHPC, suppressed local excitotoxicity, and decreased Aβ load and tauopathy. To identify additional novel compounds capable of enhancing glutamate transporter expression and activity, we collaborated with Professor Rui Chang at the US to develop an AI-based drug prediction model. This model identified two novel compounds, coded as GX and TrY, which, like RLZ, enhanced glutamate uptake in glial cultures. Daily injection (i.p.) of GX or TrY for 35 days increased GLAST and GLT-1 levels, improved memory performance, and mitigated AP load and tauopathy in the dHPC of 15-month-old 3xTg-AD mice. However, these two drugs alleviated not only tauopathy but also amyloidosis, suggesting that other cell types expressing GLAST and GLT-1, such as microglia, may contribute to AP clearance. The results showed that both drugs enhanced phagocytosis of Aβ oligomers in microglia. In summary, our findings support our hypothesis that excitotoxicity caused by EAAT1/2-related defects in glutamate clearance represents a pathogenic link between "A" and "T". Our findings also offer potential drug choices that may arrest the $A^+/T^- \rightarrow A^+/T^+$ transition.

Title of Project: Investigating ACD Regulators (INSC/LGN/PAR3) in Mediating Microtubule Stability for PNS Degeneration

Project No.: NHRI-EX114-11228NI
P.I.: Chih-Chiang Chan/詹智強
Key Professional Personnel: Chih-Chiang Chan/詹智強, Cheng-Tsung Hsiao/蕭丞宗
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

PAR3/INSC/LGN form an evolutionarily conserved complex required for asymmetric cell division in the developing brain, but its post-developmental function and disease relevance in the peripheral nervous system (PNS) remains unknown. We mapped a new locus for axonal Charcot–Marie-Tooth disease (CMT2) and identified a missense mutation c.209 T > G (p.Met70Arg) in the INSC gene. Modeling the INSCM70R variant in Drosophila, we showed that it caused proprioceptive defects in adult flies, leading to gait defects resembling those in CMT2 patients. Cellularly, PAR3/INSC/LGN dysfunction caused tubulin aggregation and necrotic neurodegeneration, with microtubule-stabilizing agents rescuing both morphological and functional defects of the INSCM70R mutation in the PNS. Our findings underscore the critical role of the PAR3/INSC/LGN machinery in the adult PNS and highlight a potential therapeutic target for INSC-associated CMT2.

1. Molecular Mechanism of the INSC p.M70R Mutation in Peripheral Neuropathy: The p.M70R mutation in the INSC gene is closely associated with sensory-motor peripheral neuropathy (CMT2), where patients exhibit motor impairment and gait instability. Research shows that this mutation weakens the binding of INSC to LGN, impacting the assembly and function of the PIL complex and significantly reducing INSC protein expression in older patients. To investigate this effect, a Drosophila model simulating the p.M70R mutation was created, revealing that this mutation-induced dysfunction correlates with age-dependent worsening of motor impairment and abnormal microtubule aggregation in sensory organs.

2. Role of Microtubule Instability in Neurodegeneration: INSC deficiency in the Drosophila model leads to increased microtubule aggregation, especially in microtubule-rich areas of sensory neurons, which correlates with neuronal degeneration and decreased motor ability. The study found that the microtubule instability caused by the p.M70R mutation is likely a primary factor in motor function decline, with motor deficits and microtubule aggregation worsening with age. This finding underscores the importance of microtubule stability in maintaining neuronal health.

3. Therapeutic Potential of Microtubule-stabilizing Agents: Microtubule stabilizers Paclitaxel (Taxol) and Cevipabulin demonstrated potential in enhancing microtubule stability in the Drosophila model. The study showed that low doses of Taxol and Cevipabulin significantly reduced abnormal microtubule aggregation in mutant flies and improved their motor abilities; conversely, higher doses exhibited toxicity. Similar effects were observed in SH-SY5Y human neuronal cells, where Taxol reduced the microtubule deacetylation caused by the p.M70R mutation, supporting microtubule stabilizers as potential therapeutic options for treating such neurodegenerative conditions.

Title of Project: Transcranial Focused Ultrasound(TFUS) Neuromodulation on Epilepsy: from Epileptogenic Network Investigation to Intervention for Drug-resistant Epilepsy

Project No.: NHRI-EX114-11229NI

P.I.: Hsiang-Yu Yu/尤香玉

Key Professional Personnel: Hsiang-Yu Yu/尤香玉, Chien-Chen Chou/周建成, Yen-Cheng Shih/施彥丞, Cheng-chia Lee/李政家, Wen-Jui Kuo/郭文瑞

Affiliation/Institution: Taipei Veterans General Hospital

Entire Project Period: From 2023 to 2025 (Total: 3 years)

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Drug-resistant epilepsy (DRE) brings negative impact on patients' quality of life and social function. Resective surgery is a good solution for surgery remediable cases. However, resective surgery is not suitable for every case of DRE. Neuromodulation is an alternative way to reduce seizure burden for patients with DRE. In addition to electric stimulation (vagus nerve stimulation, deep brain stimulation, transcranial direct current stimulation) and magnetic stimulation (transcranial magnetic stimulation), transcranial focused ultrasound (tFUS) is an emerging brain stimulation which has a novel mechanisms (mechanical and thermal) and less invasiveness over present brain stimulation methods. Our group has finished a phase one study of tFUS neuromodulation for patients with DRE with concomitant intracranial EEG (iEEG) recording. The iEEG showed power change after tFUS treatment. It has potential in the treatment of DRE. We would like to extend our research to investigate the epileptogenic network modulated by tFUS, via using corticocortical evoked potential (CCEP) and to evaluate the efficacy of neuromodulation via functional neuroimaging for epilepsy developed by our group. There are two specific aims in this study. In Aim 1, adult patients who have finished their stereo-EEG recording with a conclusion of seizure onset zone (SOZ) will be recruited. We will perform single-pulse CCEP to DRE patients before and after a 5- minute tFUS stimulation. The second aim was to evaluate the treatment effect of tFUS by using a new EEG-fMRI method developed and validated in our group, the fast fMRI acquisition (ten brain volumes per second) in concurrent EEG-fMRI recording to sensitively and accurately delineate the irritative zone by reducing EEG artifacts. In our phase II trial, a single blind, randomized crossover study enrolled 12 patients to evaluate the safety and efficacy of tFUS neuromodulating treatment for patients with drug resistant epilepsy. We collected the data of EEG-fMRI before tFUS treatment and hours after tFUS treatment. Seven cases (3 male, 4 female, age 21-56 years) completed the EEG-fMRI examination. One of the cases who showed response to tFUS whose seizure was from the left temporal lobe. The default mode connectivity seemed to show reduced connectivity with brain regions in the temporal lobe after tFUS treatment. A reduction of salience network was also noted. Further analysis was ongoing and will be shown in the meeting.

Title of Project: Investigating the Causal Mechanism of Developmental Anomaly of the Corpus Callosum in Neuropsychiatric Disorders

Project No.: NHRI-EX114-11230NI
P.I.: Guey-Shin Wang/王桂馨
Key Professional Personnel: Lee-Hsin Wang/王李馨
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2023 to 2025 (Total: 3 years)

The corpus callosum connects the left and right hemispheres and functions in integration, transfer and processing of the sensory, motor and cognitive information from both hemispheres. Defects in the corpus callosum is the most common pathological feature among neurological diseases including neurodegenerative, neurodevelopmental and neuropsychiatric diseases. Corpus callosum atrophy is strongly associated with cognitive decline in neurodegenerative diseases, whereas partial agenesis of the corpus callosum is commonly seen in neurodevelopmental and psychiatric disorders, suggesting a possibility for the callosal projection neuron with an intrinsic vulnerable characteristic. However, the cause of predisposition to malformation or breakdown of the corpus callosum in neurological diseases remains undetermined. The cognitive impairments of myotonic dystrophy type 1 (DM1) include mental retardation, autism spectrum disorder (ASD), depression, attention deficit hyperactivity disorders (ADHD), and neurodegeneration. Hypoplasia and atrophy of the corpus callosum are the major feature of DM1 brain. The genetic basis of DM1 is caused by an expansion of CTG repeats in the 3' untranslated region (UTR) of the Dystrophia Myotonica Protein Kinase (*DMPK*) gene. *DMPK* mRNA containing expanded CUG repeats accumulates in nuclear foci and disrupts functions of at least two families of RNA binding proteins: muscleblind like (MBNL) and CUGBP Elav-like family member (CELF) proteins. To understand the impact of expanded CUG (CUG^{exp}) RNA on the cortical development, we established a mouse model, EpA960/$Emx1^{IRES\mathit{cre}}$, for expression of CUG^{exp} RNA in neural progenitors of the dorsal telencephalon during neurogenesis. EpA960/$Emx1^{IRES\mathit{cre}}$ animals exhibited features of congenital DM1 including hypoplasia of the corpus callosum and impairment in learning and memory. Expression of CUG^{exp} RNA induced cell death in neural progenitors resulted in reduced generation of callosal projection neurons (CPNs). Transcriptome analyses of EpA960/$Emx1^{IRES\mathit{cre}}$ embryonic brains at two distinct stages, neuroepithelial expansion at E10.5 and initiation of neurogenesis at E13.5, revealed that down-regulation of genes involved in cell proliferation and differentiation were commonly observed at both stages, whereas dysregulations of genes in regulating glucose catabolism and development of the corpus callosum were seen at E10.5 and E13.5 respectively. Using publicly available scRNA-seq data, we established the transcriptome profiles of developing mouse cortex for examining the developmental trajectories of those differentially expressed genes related to metabolism and CPN development and identifying the potential subclusters of CPNs. The signatures of the potential subclusters will be used as the reference to identify the characteristics of cells that are susceptible to CUG^{exp} RNA-induced cell death. Currently, animals carrying GFP fluorescence reporter are ready for generating EpA960/$Emx1^{IRES\mathit{cre}}$-GFP and $Emx1^{IRES\mathit{cre}}$-GFP embryos and single cells isolated from the dorsal telencephalon of embryos at E10.5 and E13.5 will be used for sequencing. By comparison of the results with the established referenced transcriptome profiles will help identify the population of susceptible progenitors and the intrinsic characteristics.

Title of Project: Modulation of Emotional Valence and Emotion Processing in Human Empathy
Project No.: NHRI-EX114-11231NI
P.I.: Ming-Tsung Tseng/曾明宗
Key Professional Personnel: Min-Min Lin/林敏敏, Zhilin Su/蘇致霖, Ming-Tsung Tseng/曾明宗
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Empathy, the capacity to share emotional states of others, plays a crucial role in successful social interaction and psychological well-being. In contrast, socially driven incongruent emotions, including gluckschmerz (unpleasantness to others' fortunes) and schadenfreude (pleasantness to others' misfortunes), may influence the formation of positive impressions and social bonding. Previous studies indicated that social comparison, the process of evaluating oneself through comparing with a standard, affected empathic responses in social contexts, while the underlying mechanisms remained largely unclear. The present study aimed to investigate how socially driven incongruent emotions modulate human empathy. We designed an empathy-for-pain paradigm to induce gluckschmerz and schadenfreude in different social comparison contexts and examined how they modulated empathy. In fMRI study 1, we recruited 46 healthy participants and found that when participants experienced a worse pain outcome than the confederate (i.e., upward social comparison), neural activity in anterior insular cortex and dorsal anterior cingulate cortex increased, which predicted the reduction of positive empathic responses. This effect was fully mediated by envy. In fMRI study 2, we recruited 48 healthy participants and measured their empathic responses in competitive contexts. In upward social comparisons, where participants lost the competition, they expressed gluckschmerz and schadenfreude responses that countered the corresponding positive and negative empathic responses to the confederate's pain outcome. In contrast, when they won the competition, they reported increasing schadenfreude, which countered negative empathy to the confederate's misfortune. In addition, participants' likeability ratings were modulated by the gluckschmerz and schadenfreude responses after the competition task, suggesting that social comparisons influenced the perception of others' impressions via counter-empathy processing. In fMRI study 3, we so far have recruited 7 participants with depressive symptoms and preliminarily found that participants' empathic responses were reduced relative to health controls, probably accounted for by the narrowed social engagement due to self-generated negative affect. Taken together, these findings not only enhance our understanding about the modulation of socially driven emotions on human empathy, but provide insights into the impaired social interaction in relevant affective disorders.

Title of Project: Dissect Cerebellar Mechanism and Therapeutics of Tremor Subtypes by Spatio-temporal Neural Dynamics

Project No.: NHRI-EX114-11303NI
P.I.: Ming-Kai Pan/潘明楷
Key Professional Personnel: Wen-Chuan Liu
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Essential tremor (ET) is the most common movement disorder, characterized primarily by action tremor. Despite its prevalence, therapeutic responses are varied and often unsatisfactory, indicating multiple underlying pathophysiologies for different ET subtypes. Less than 50% of ET patients respond to pharmacological therapy, and no new medications have been developed in the past 25 years. From 2023 to 2024, six pharmaceutical companies reported unsuccessful clinical trials for ET medications, collectively spending over one billion US dollars. This highlights the urgent unmet medical need for effective ET therapies and a new understanding of the pathophysiology underlying drug-refractory ET.

In this project, we aim to elucidate two potential mechanisms that could explain the dichotomy in drug responses. Our primary objective is to uncover the circuitry dynamics that underlie the pathophysiology of each ET subtype. Additionally, we aim to design novel therapeutic approaches based on the underlying pathophysiology of drug-refractory ET subtypes. We utilized two mouse models for ET: the harmaline-induced tremor model, which facilitated the discovery of propranolol and primidone 25 years ago, and the *Grid2*^{dupE3} mouse model identified by our group, which exhibits ET-like climbing fiber (CF) overgrowth in the cerebellum (*Science Translational Medicine*, 2020, 2024).

In the 1.5 years, we observed that harmaline-induced tremors responded to both propranolol and primidone, while tremors in *Grid2*^{dupE3} mice were refractory to both medications. We then investigated whether the two models encode tremor frequency through distinct mechanisms. Using in-vivo electrophysiology, both models exhibited similar cerebellar population activity for frequency coding, which cannot explain their diverse pharmacological responses. Using two-photon calcium imaging to study population synchrony of Purkinje cells (PCs), we found that harmaline and *Grid2*^{dupE3} mice showed regional versus global synchrony of PCs, respectively, suggesting a potential candidate to explain differential drug responses. To address this, we built cerebellar computational models of harmaline- versus *Grid2*^{dupE3}-like models, confirming that harmaline mice use IO neurons as pacemaking cells for tremor generation, and thus are sensitive to propranolol therapy. In contrast, *Grid2*^{dupE3} mice develop self-sustained olivocerebellar oscillations due to climbing fiber overgrowth and global synchrony for tremors and are independent of IO pacemaking and propranolol therapy.

In the next year, we will use the computation model to test novel candidate drug targets and performed preclinical drug therapy.

Title of Project: The Gut–brain Axis Underlying Comorbid Anxiety Disorders in Inflammatory Bowel Disease

Project No.: NHRI-EX114-11309NI
P.I.: Kuei-Sen Hsu/許桂森
Key Professional Personnel: Chin-Hao Chen/陳晉豪, Yu-Yu Chang/張又予
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Anxiety symptoms are commonly observed in individuals with inflammatory bowel disease (IBD), but the mechanistic link between IBD and comorbid anxiety remains incompletely understood. Our previous study revealed that vagal gut-brain signaling contributes to driving comorbid anxiety-like behaviors in dextran sulfate sodium (DSS)-induced colitis mice, but how the vagus nerve senses and transmits information to the brain in response to changes in the colonic microenvironment following DSS treatment remains elusive. Here, we identify a critical contribution of pro-inflammatory $CD86^+$ macrophages to activate gut-innervating vagal afferents and ultimately drive anxiety-like behaviors in DSS-treated mice. An increased number of $F4/80^+$ macrophages accumulated closely with gut-innervating vagal afferent fibers following DSS treatment. Depletion of macrophages alleviated DSS-induced anxiety-like behaviors, whereas peripheral delivery of lipopolysaccharide-activated M1 macrophages promoted anxiety-like behaviors, which were prevented by bilateral vagal afferent ablation. Moreover, differential expression levels of anxiety-like behaviors were positively correlated with neuronal activity changes in the nucleus tractus solitarius, locus coeruleus, and basolateral amygdala. Finally, treatment with either anti-$\alpha4\beta7$ integrin antagonist vedolizumab or neutralizing anti-interleukin-1β monoclonal antibody effectively alleviated DSS-induced anxiety-like behaviors. Collectively, these findings unravel a mechanism of macrophage-to-vagus nerve communication via cytokine signaling responsible for comorbid anxiety associated with experimental colitis and suggest that pro-inflammatory $CD86^+$ macrophages may represent a potential therapeutic target for psychological comorbidities in patients with IBD.

Title of Project: Exploration of the Metabolic Mechanisms of the Electrophysiological Biomarkers for Response to Methylphenidate Treatment in Children with Attention-deficit/hyperactivity Disorder

Project No.: NHRI-EX114-11310NI
P.I.: Chi-Yung Shang/商志雍
Key Professional Personnel: Ming-Hsien Hsieh/謝明憲, Susan Shur-Fen Gau/高淑芬
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Objective: This study investigated how 12-week teatment of methylphenidate influenced brain function and cognitive processes in children diagnosed with ADHD, with the goal of identifying biomarkers that reflected the medication's impact.

Method: To date, we have recruited 34 children with ADHD and 41 typically developing children (TDC) were recruited. We assessed the behavioral problems and cognitive functions by ADHD Rating Scale-IV (ADHDRS-IV), Clinical Global Impression - Severity scale (CGI-S) and Continuous Performance Test (CPT). A 12-week methylphenidate treatment was administered to children diagnosed with ADHD. To evaluate brain activity, resting-state electroencephalography (EEG) was conducted on both the ADHD group and the TDC group, with assessments carried out prior to treatment initiation and again following the 12-week period.

Results: Before treatment, children with ADHD exhibited notably higher levels of inattention, hyperactivity/impulsivity, and CGI-S scores compared to TDC. They also showed reduced performance on the CPT, specifically with slower reaction times and greater variability in response speed. Following 12 weeks of methylphenidate administration, these differences between the ADHD and TDC groups were no longer statistically significant across measures of inattention, hyperactivity/impulsivity, CGI-S, reaction time (RT), and reaction time standard deviation (RTSD). Electrophysiological data further revealed enhancements in peak alpha frequency and eigenvector centrality within the ADHD group, indicating improvement in neurophysiological activity.

Conclusions: Following 12 weeks of methylphenidate administration, children with ADHD showed marked improvements in both cognitive performance and brain function. These findings highlight the potential of neuropsychological assessments and electrophysiological indicators as valuable biomarkers for the effects of medication on ADHD.

Title of Project: Targeting ALS by a Novel Conserved Motor Neuron Micropeptide Derived from LncRNA

Project No.: NHRI-EX114-11330NI
P.I.: Jun-An Chen/陳俊安
Key Professional Personnel: Fang-Yu Hsu/許芳瑜
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

The presence of small open reading frame (smORF)-encoded micropeptides within long non-coding RNA (lncRNA) regions is often underappreciated due to their limited size and scarcity. However, emerging evidence has shed light on their roles in fundamental biological processes, although their contribution to neural development and neurodegeneration remains unclear. To address this knowledge gap, we used spinal motor neurons (MNs) as a paradigm to investigate the function of a murine micropeptide, Sertm2, which is encoded by the lncRNA *A730046J19Rik*, during MN development. Our preliminary results indicate that this micropeptide is a highly conserved putative transmembrane protein expressed abundantly in postmitotic MNs. Interestingly, genetic deletion of *A730046J19Rik* from MN subtypes induced retrograde signaling of muscle neurotrophic Glial cell line-derived neurotrophic factor (GDNF), revealing that the Sertm2 micropeptide may modulate this signaling pathway. In addition, our experiments on a mouse model of ALS support that reducing *A730046J19Rik* levels by genetic ablation could significantly extend the lifespan of affected mice, indicating the potential for *Sertm2/A730046J19Rik* as a new therapeutic target for neurodegenerative diseases such as ALS. Therefore, we systematically identify micropeptides in spinal MNs, verify their expression *in vivo*, and then use *Sertm2/A730046J19Rik* as a paradigm to elucidate the role of lncRNA-derived micropeptides in neural development and neurodegeneration. Collectively, our results may provide the first comprehensive blueprint of the micropeptidome in spinal MNs and open up new avenues for targeting micropeptides as potential therapeutics against neurodegenerative diseases.

Title of Project: Investigating the Role of CCK Interneurons in the Dentate Gyrus: Implications for Cannabinoid Effects on the Circuitry, Cognition, and Emotion

Project No.: NHRI-EX114-11432NI

P.I.: Cheng-Chang Lien/連正章

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2022 to 2025 (Total: 4 years)

Background and aim: The transient receptor potential melastatin 2 (TRPM2) ion channel has emerged as a key transducer of temperature and oxidative stress signals. Its strategic expression in neurons, microglia, and leukocytes positions it at the intersection of neuroinflammation and immune responses. Here, we hypothesize that TRPM2 serves as a central mediator driving the pathogenesis of inflammation-associated neurocognitive disorders. Our study seeks to elucidate the cell-specific roles of TRPM2 across diverse cellular populations in these conditions.

Methods: To investigate the role of TRPM2 in inflammation-associated neurocognitive disorders and evaluate the impact of sex hormones on these conditions, we conducted a comprehensive study using both global and conditional knockout (KO) mice models. Conditional KOs were generated by crossing STOCK *Trpm2*$^{tm1.1Dpc}$/J mice with Cre lines targeting cortical neurons (STOCK Tg(Actl6b-Cre)4092Jiwu/J), microglia (C57BL/6-*Tmem119*$^{em1(cre/ERT2)Gfng}$/J), and hematopoietic cells (B6.Cg-*Commd10*$^{Tg(Vav1-icre)A2Kio}$/J). Inducible deletion of TRPM2 in microglia was achieved via tamoxifen administration. Inflammation was induced using lipopolysaccharide (LPS), while sex hormone influences were evaluated by administering 4-Vinylcyclohexene dioxide (VCD) and testosterone undecanoate. We also compared the effects of TRPM2 global knockout between male and female mice. Cognitive function was assessed using the Barnes Maze test, and motor coordination was evaluated with rotarod and pole tests. Cre-driver lines were validated by crossing them with tdTomato reporter (B6.*Cg-Gt(ROSA)26Sor*$^{tm9(CAG-tdTomato)Hze}$/J) mice. STOCK *Trpm2*$^{tm1.1(icre)Jsmn}$/J mice were crossed with tdTomato reporter mice to delineate expression profiles of TRPM2.

Results: We observed significant sex-dependent differences in cognitive performance after LPS injections following global TRPM2 deletion. Male mice with global TRPM2 knockout exhibited better performance on the Barnes Maze compared to their littermates with intact TRPM2. However, this protective effect was not observed in female mice. Furthermore, female mice treated with VCD and testosterone undecanoate showed significantly worse cognitive performance. Among conditional KO mice, deletion of TRPM2 in microglia or cortical neurons resulted in better cognitive performance, while deletion in hematopoietic cells led to worse performance compared to littermate controls.

Conclusion: Our findings reveal sex-specific roles of TRPM2 in mediating inflammation-associated neurocognitive disorders. Specifically, TRPM2 expression in cortical neurons and microglia appears detrimental in inflammation-associated neurocognitive disorders, while its expression in hematopoietic cells confers protective effects. These insights underscore the complex and nuanced involvement of TRPM2 in neuroinflammation and immune responses, highlighting potential therapeutic targets for inflammation-associated neurocognitive disorders.

Title of Project: Mechanism of Tight Junction Protein ZO-1 Mediating Spindle Misorientation, Chromosomal Instability and Its Role in Colorectal Carcinogenesis

Project No.: NHRI-EX114-11204BC

P.I.: Wei-Ting Kuo/郭瑋庭

Key Professional Personnel: Yi-Syuan Tsai/蔡依璇, Ying-Chieh, Chang/張映捷, Chia-Ying Lin/林家瑩, Hsuan-Yu Chen/陳宣妤

Affiliation/Institution: National Taiwan University

Entire Project Period: From 2023 to 2026 (Total: 4 years)

Background: Tight-junction scaffolds not only seal epithelial layers but also convey polarity signals to the mitotic apparatus. We hypothesized that the tight junction protein ZO-1 (*TJP1*) acts as a molecular pivot orienting the mitotic spindle with the apical-basal axis to prevent chromosomal instability (CIN). Given that CIN is an established contributor of colorectal cancer (CRC) progression, elucidating how ZO-1 dysfunction disrupts spindle topology may uncover a potential susceptibility. **Aim:** We investigated if ZO-1 loss induces spindle misorientation, DNA damage, and tumor proliferation in colorectal cancer by the integration of patient tissue analysis, a conditional knockout animal model, and domain-specific rescue in intestinal epithelial cells. **Results:** In human specimens, immunofluorescence and qPCR demonstrated a reduction in ZO-1 protein and transcript levels in colorectal cancer compared to matched normal mucosa. Concurrently, E‑cadherin and β‑catenin were diminished, whereas proliferating‑cell nuclear antigen (PCNA) and the DNA‑damage marker γ‑H2A.X increased, associating ZO‑1 loss with both junctional disintegration and chromosomal instability. In conditional knockout murine models, intestinal-specific ZO-1-null animals (ZO-1 KO^{IEC}) subjected to azoxymethane and dextran-sodium-sulfate exhibited a tumor burden comparable to that of wild-type counterparts, with larger lesions, and no differences in weight or colon length. Histological examination revealed high-grade dysplasia, spindle orientation exceeding 30°, misaligned α-/γ-tubulin, and numerous γ-H2A.X foci in both tumor and adjacent normal tissues, thereby showing a direct *in vivo* connection between ZO-1 loss, spindle disorganization, and genomic damage. *In vitro* study showed that CRISPR/Cas9 editing generated ZO‑1‑null Caco‑2 monolayers that exhibited spindle misalignment, an increase in sub-G1 apoptosis, and an elevation in γ‑H2A.X signal. The elimination of the domain demonstrated that the N-terminal motif was essential for spindle orientation, while the ablation of ABR and U5-GuK domains reinstated single-lumen formation. Pharmacological interference with actin polymerization (latrunculin A, cytochalasin B, jasplakinolide) or myosin II function (blebbistatin) did not restore spindle misorientation or γ‑H2A.X accumulation, thereby dissociating the phenotype from ZO-1/actomyosin interaction. Inhibiting caspase-3 with z‑DEVD‑FMK did not reduce γ‑H2A.X, suggesting that DNA damage occurs prior to apoptosis, rather than after to it. Most importantly, proximity-ligation experiments demonstrated the colocalization of ZO-1 and AKAP9 (a regulator of microtubule dynamics known to affect the mislocalization of blood-testis barrier proteins, including ZO-1) in wild-type cells. The absence of ZO-1 mislocalized AKAP9, compromised the location of the γ-tubulin, establishing a mechanistic connection between tight junction failure and spindle misorientation. **Conclusions:** Our comprehensive research reveals that ZO-1 serves as a protector of chromosomal integrity: its N-terminal domain facilitates spindle alignment and minimizes DNA breakage. The disruption of the ZO-1-centrosome interaction triggers chromosomal instability, accelerating colitis-associated tumorigenesis in mice and characterizing human colorectal cancer foci with a unique low ZO-1 and high γ-H2A.X signature. These findings reclassify TJ disassembly from a passive outcome to a proximal facilitator of colorectal cancer and identify the ZO‑1/AKAP9 interface as a potential therapeutic target for preventing genome-destabilizing early events.

Title of Project: Exploiting PHF8-mediated Epigenetic Dependency in Gastric Cancer
Project No.: NHRI-EX114-11211BI
P.I.: Wen-Ching Wang/王雯靜
NHRI Researcher: Chiou-Hwa Yuh/喻秋華
Key Professional Personnel : Ding-Jun Huang/黃鼎鈞, Tsan-Jan Chen/陳粲然, Chung-Yung Ma/馬崇勇
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Epigenetic Vulnerabilities in Gastric Cancer: PHF8-Driven PKCα–Src Signalling as a Druggable Axis

Gastric cancer (GC), the world's fifth most common malignancy, remains difficult to treat once advanced. Utilizing public cohorts (OncomineTM, KM-plotter) and our multi-omic datasets, we identify the histone lysine demethylase PHF8 as a crucial epigenetic driver of gastric cancer progression. PHF8 is markedly over-expressed in tumours relative to normal mucosa, and its high expression correlates with poorer overall survival and earlier disease progression. ChIP-seq confirms co-occupancy of PHF8 and the repressive mark H3K9me3 at these loci, underscoring its chromatin-remodelling role. Mechanistically, PHF8 recruits c-JUN to up-regulate PRKCA (PKCα) and MKRN1, an E3 ligase that ubiquitinates and destabilises PTEN, thereby driving the PKCα–Src axis, mitochondrial dysfunction, and invasive behaviour. PHF8 depletion restores PTEN stability and suppresses tumour growth. An AI-guided drug screen uncovers a synergistic midostaurin-bosutinib combination that blocks the PHF8–MKRN1 pathway, inhibits migration *in vitro*, and impedes zebrafish xenograft expansion, with enhanced efficacy in MKRN1-deficient cells. These findings establish PHF8-centred chromatin demethylation as a tractable vulnerability in GC and highlight dual-kinase inhibition as a precision therapeutic strategy to exploit this epigenetic-metabolic axis.

Title of Project: Impact of PD-1 Post-translational Modifications and Trafficking in T Cells on Cancer Progression

Project No.: NHRI-EX114-11212BI
P.I.: Yi-Ching Wang/王憶卿
Key Professional Personnel: Yi-Ching Wang/王憶卿
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Immune checkpoint inhibitor (ICI) therapies targeting programmed cell death-1 (PD-1) have revolutionized cancer treatment by reactivating exhausted T cells and restoring anti-tumor immunity. Despite their clinical success, a significant subset of patients exhibits resistance or limited response to these therapies. Understanding the regulatory mechanisms controlling PD-1 expression and function is essential to overcome therapeutic resistance and improve outcomes. Our recent studies uncover three critical post-translational mechanisms that sustain T cell exhaustion in the lung tumor microenvironment (TME) through the modulation of PD-1. First, we identified the small GTPase Rab37 as a vesicular trafficking mediator that dynamically regulates PD-1 plasma membrane presentation in a GTP- and glycosylation-dependent manner. Elevated Rab37 expression in CD8+ T cells correlates with increased PD-1/TIM3 co-expression and poor survival in lung cancer patients, highlighting Rab37+/PD-1+/TIM3+ T cells as a novel prognostic biomarker. Second, we demonstrated that USP24, a deubiquitinase transcriptionally induced by IL-6/STAT3/NF-κB signaling, stabilizes PD-1 by removing K48-linked polyubiquitin chains. Genetic ablation or pharmacological inhibition of USP24 enhances CD8+ T cell cytotoxicity and synergizes with anti-CTLA4 therapy to suppress lung tumor growth *in vivo*. Clinically, high infiltration of USP24+/PD-1+/Lag3+ CD8+ T cells was associated with poor prognosis and immunotherapy resistance. Thirdly, the high IL-6 in the TME of progressive tumors induces the JAK/STAT3 signaling pathway in cancer cells or tumor-infiltrating leucocytes. We preliminarily showed that IL-6-mediated JAK2 activation phosphorylated PD-1 at Y223 and Y248 (p-Y223, p-Y248). Y223F and Y248F mutations decreased PD-1 protein stability, suggesting that p-Y223 or p-Y248 is critical in T cell suppression and PD-1 stabilization. We are characterizing the crosstalk of phosphorylation and deubiquitylation in controlling PD-1 stability driven by IL-6 stimulation. These findings elucidate a coordinated network of PD-1 trafficking and stabilization governed by Rab37, USP24, and IL6/JAK2, underscoring their significance in sustaining T cell exhaustion and immune suppression. Targeting the Rab37/PD-1 vesicle axis, USP24-mediated deubiquitination, and IL6/JAK2 signal represents a promising strategy to improve the efficacy of ICI therapies in lung cancer.

Title of Project: Targeting ER Protein TXNDC5 in the Tumor Stroma: Implications for Tumorigenesis and Therapy Against Colorectal Cancer

Project No.: NHRI-EX114-11213BI
P.I.: Kai-Chien Yang/楊鎧鍵
Key Professional Personnel: 程凱琳，林瑜珊
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Mesenchymal-type colorectal cancer (CRC) is resistant to immunotherapy and associated with poor outcomes, largely driven by cancer-associated fibroblasts (CAFs)-mediated stromal infiltration and immune tolerance. This study explores the role of thioredoxin domain-containing protein 5 (TXNDC5), a protein disulfide isomerase contributing critically to organ fibrosis through activating fibroblasts and extracellular matrix production, in mesenchymal-type CRC. TXNDC5 was highly expressed in stromal fibroblasts in both human and mouse CRC. Fibroblast-specific TXNDC5 deletion reduced CAF activation, tumor fibrosis, and overall tumor burden in an azoxymethane/dextran sulfate sodium (AOM/DSS)-induced CRC model exhibiting mesenchymal traits. Mechanistically, TXNDC5 enhanced TGFβ signaling by stabilizing TGFBR1 in CAFs. Loss of TXNDC5 in CAFs attenuated desmoplasia, leading to decompressed tumor vessels, reduced intra-tumoral hypoxia and increased cytotoxic T cell infiltration. TXNDC5 deletion in CAFs potentiated anti-tumor effects of PD1 blockade in AOM/DSS-induced CRC. These findings reveal an important yet previously unrecognized role of fibroblast TXNDC5 in CRC progression and suggest that targeting TXNDC5 in CAFs could be a powerful new therapeutic strategy treating CRC.

Title of Project: Develop IL-19 Antibody Immunotherapy and Unravel Immunosuppressive Mechanism in Peritumoral Region of Glioblastoma by Single Cell Transcriptome Analysis

Project No.: NHRI-EX114-11214BI
P.I.: Cheng-Yu Chen/陳震宇
Key Professional Personnel: Gilber Aaron Lee/李爾博, Yu-Wei Chang/張育維
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

IL-19 is an immunosuppressive cytokine and associated with poor survival in patients with GBM. This study aims to develop a novel human IL-19 nanotheranostic probe to detect IL-19 expression in TMZ-resistant GBM. We synthesized a magnetic resonance imaging (MRI) contrast agent that can specifically target the IL-19 of brain cancer cells and evaluate its ability as a targeted drug delivery system. Previous study identified that IL-19 is a predicted immune suppressive cytokine in peritumoral region and was associated with poor survival in patients with GBM. Cholesterol (CHOL)-Polyethylene glycol (PEG)-SH were used to modify superparamagnetic iron oxide (SPIO) conjugated with IL-19 antibodies to obtain CHOL-PEG-SPIO-IL19 nanoparticles. CHOL-PEG-SPIO-IL19 nanoparticles were uniformly spherical under the transmission electron microscope (TEM), with regular morphology and good dispersion, which presented with a size of 17.3 ± 1.6 nm. In addition, the hydrodynamic size and zeta potentials of CHOL-PEG-SPIO-IL19 nanoparticles were 121.4 ± 7.8 nm and -11.4 ± 6.1 nm used dynamic light scattering (DLS) technique. Indeed, the CHOL-PEG-SPIO-IL19 exhibited a specific binding capacity to IL-19 of the human glioblastoma cell line (DBTRG). MRI imaging demonstrated enhanced targeting efficiency in brain tumors, with *in vivo* studies showing prominent hypointense areas in T2*-weighted MRI scans of tumor-bearing mice injected with CHOL-PEG-SPIO-IL-19, highlighting nanoparticle presence in IL-19-expressing regions. Prussian blue staining further confirmed the localization of these nanoparticles in tumor tissues, verifying their potential as a diagnostic tool for detecting IL-19 expression in glioblastoma. This system offers a diagnostic imaging for IL-19-expressing GBM.

Title of Project: Deciphering the Mechanism and Clinical Significance of Cetuximab Resistance-mediated Microenvironmental Remodeling and Immune Checkpoint Inhibitor Resistance in Head and Neck Cancer

Project No.: NHRI-EX114-11215BI
P.I.: Muh-Hwa Yang/楊慕華
Key Professional Personnel: Po-Hsien Chiu/邱柏憲
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

This study illuminates a critical link between cetuximab resistance and impaired efficacy of immune checkpoint inhibitors (ICIs), a phenomenon observed in patients with prior cetuximab exposure. Our cellular investigations in HNSCC models showed an initial burst of inflammation (upregulation of IFN-\alpha and IFN-\gamma stimulated genes) upon cetuximab treatment, which unexpectedly faded with continued exposure, suggesting a negative feedback loop. We developed a cetuximab resistance signature that robustly predicted ICI non-response, establishing a common pathway for these resistance mechanisms.

Crucially, we identified a novel acetylation event at Lys637 on the STAT1 protein as a key modulator. We demonstrated that STAT1-K637 acetylation impairs STAT1's transcriptional activity by reducing its dimeric Tyr701 phosphorylation, thereby dampening the beneficial inflammatory response. Translating these findings to the clinic, we developed a specific antibody for STAT1-K637 acetylation. Its application to patient samples revealed a significant enrichment of STAT1-K637 acetylation in individuals experiencing disease progression and non-response to ICIs. Furthermore, higher levels of this acetylation correlated with poorer overall and progression-free survival in ICI-treated patients. Our work collectively identifies that while cetuximab initially triggers inflammation, STAT1-K637 acetylation compromises this crucial anti-tumor immune response, offering a novel biomarker to predict ICI outcomes and guide therapeutic strategies.

Title of Project: Cancer Initiation and Progression of Ovarian High-grade Serous Carcinoma Originating from the Oviduct: Role of Ovulation

Project No.: NHRI-EX114-11216BI

P.I.: Tang Yuan Chu/朱堂元

Key Professional Personnel: Hsuan-Shun Huang/黃玄舜, Kanchana Subramani

Affiliation/Institution: Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

Entire Project Period: From 2023 to 2025 (Total: 3 years)

Compelling epidemiological evidence, particularly the three-decade protective effect of oral contraceptives, establishes ovulation as a critical driver of ovarian cancer initiation. High-grade serous carcinoma (HGSC), the most prevalent and aggressive ovarian cancer subtype, originates in the fallopian tube fimbria epithelium (FTE) through exposure to carcinogenic components in ovulatory follicular fluid (FF). Our previous work identified FF's multifaceted transforming capabilities, including inducing TP53 mutagenesis, promoting stemness, facilitating clonal expansion, and driving malignant transformation. We further demonstrated that postovulatory progesterone exerts protective effects by inducing necroptosis in p53-mutated FTE cells through progesterone receptor (PR) signaling.

In this study, we developed a novel PPC genetically engineered mouse (GEM) model featuring sequential induction of: (1) Trp53 R172H mutation (P), (2) Pgr deletion (P), and (3) Ccne1 overexpression (C). This model recapitulates the stepwise progression from early p53 signatures to serous tubal intraepithelial carcinoma (STIC) and ultimately HGSC. We hypothesize that LGR6-expressing cells represent both the stem cell population and cellular origin of HGSC development in FTE, with ovulation activating LGR6-mediated stemness pathways.

Our findings reveal that FF-derived reactive oxygen species (ROS) enter FTE cells via NOX1 during ovulation, leading to oxidation and inactivation of β-arrestin. This results in selective accumulation of LGR6 (but not LGR5) GPCR protein, triggering activation of the LGR6/ZNRF3/β-catenin/TCF7L2 signaling axis. This pathway upregulates stemness genes (NANOG, OCT4) and establishes an LGR6 autoregulatory loop, significantly enhancing clonal expansion, anchorage-independent growth, and xenograft tumorigenicity in initiated FTE cells. Thus, FF-ROS promotes carcinogenesis through both TP53 mutagenesis [PMID: 39637685] and stemness pathway activation.

Current studies employing LGR6-Cre;PPC;Pgr-KO triple-transgenic mice (with LGR5-Cre controls) are providing definitive genetic validation of this dual mechanism. Despite challenges including low fertility in Pgr-KO mice and gender imbalance (29 female vs 55 male pups), we successfully generated target Lgr6-$Cre^{+/-}$;$PPC^{+/+}$;$Pgr^{-/-}$ mice. While heterozygous Pgr deletion showed no tumorigenesis, tumor development in homozygous Pgr-KO mice is under investigation. Parallel studies using oviduct organoids confirm the functional efficacy of our stepwise oncogenic induction system (Trp53 mutation → Pgr deletion → Ccne1 overexpression).

Title of Project: Decipher the Spatiotemporal Regulation of Directional Cell Migration: from Biology to Clinical Therapies

Project No.: NHRI-EX114-11217BI
P.I.: Sen-Yung Hsieh/謝森永
Key Professional Personnel: Sen-Yung Hsieh/謝森永
Affiliation/Institution: Chang Gung Medical Foundation
Entire Project Period: From 2023 to 2025 (Total: 3 years)

F-actin cytoskeleton remodeling is essential for cell migration, organ development, and immune responses. CDC42, a factor orchestrating F-actin remodeling for membrane dynamics, switches between its inactive GDP- and active GTP-bound forms. However, the biological and clinical significance of the mechanisms regulating CDC42 protein turnover remains unclear. Here we show that KLHL23-mediated CDC42·GTP polyubiquitylation for degradation and RhoGDI-mediated CDC42·GDP sequestration away from the plasma membrane co-inactivate CDC42 in a spatiotemporal context, influencing membrane dynamics and homeostasis during migration. Through a genome screen, we identified KLHL23 as a tumor-invasion suppressor inhibiting F-actin polymerization. We further confirmed KLHL23-Cul3 as the E3 ligase responsible for CDC42 polyubiquitylation and degradation. KLHL23 competes with RhoGDI for binding to the switch II region of CDC42, which further enhance the selective targeting of CDC42·GTP and CDC42·GDP, respectively. KLHL23 depletion in cells leads to F-actin and membrane over-protrusion, as well as epithelial-mesenchymal transition and tumor metastasis. Meanwhile, dysregulated KLHL23-mediated CDC42 ubiquitylation causes the developmental disorder Takenouchi-Kosaki syndrome (TKS), an autosomal dominant disorder involved in multi-organ development defects, particularly the central neural system. Germline variant Y64C-CDC42, responsible for the majority of TKS cases, evades KLHL23-mediated ubiquitylation and degradation. Fluorescence resonance energy transfer assays reveal that the KLHL23—CDC42·GTP interaction plays a primary role in quenching CDC42 activity during membrane protrusion-retraction, while the RhoGDI—CDC42·GDP interaction occurs lately. Our results demonstrate the spatiotemporal interplay between RhoGDI and KLHL23 in regulating CDC42 turnover to ensure membrane homeostasis and sustainable dynamics during migration. As KLHL23/RhoGDI—CDC42 axis dysregulation causes TKS and tumor metastasis, our findings open avenues for exploring novel therapeutics.

Title of Project: Decoding and Modulating the Immune Synaptic Interactome for Gamma Delta T Immunotherapy in Cancer

Project No.: NHRI-EX114-11218BI
P.I.: Hsing-Chen Tsai/蔡幸真
Key Professional Personnel: Chong-Jen Yu/余忠仁, Tai-Chung Huang/黃泰中, Shih-Yu Chen/陳世淯, Ying-Ta Wu/吳盈達
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Gamma delta (γδ) T cells are emerging as promising effectors in adoptive cell therapy (ACT) due to their unique ability to eliminate tumor cells through MHC-independent recognition, enabling both autologous and allogeneic applications. A central mechanism underlying their cytotoxicity is the formation of an immune synapse, a dynamic interface that facilitates the directed secretion of cytolytic granules and orchestrates signaling for target recognition and killing. Our previous studies revealed that pretreating tumor cells with DNA methyltransferase inhibitors enhances γδ T cell cytotoxicity by upregulating immune synapse–related molecules. These findings highlight the importance of the synaptic molecular landscape in determining therapeutic efficacy. To systematically characterize these synaptic components, we employed spatial optoproteomics (Microscoop™), which combines AI-based image recognition, light-induced biotinylation, and mass spectrometry. This approach enabled us to profile 631 candidate proteins localized at the immune synapse, including known receptors and signaling molecules such as LFA-1, ICAM-1, ZAP-70, and γδ TCR components. By integrating transcriptomic data with synaptic protein profiles from γδ-sensitive and γδ-resistant tumors, we identified moesin—an ERM family protein that links the plasma membrane to the actin cytoskeleton—as a candidate regulator of synapse functionality. Loss-of-function studies supported moesin's role in modulating γδ T cell–mediated killing. In addition to investigating moesin-anchored proteins, we are now exploring other potential synaptic regulators revealed by our current dataset, particularly those involved in membrane organization, mitochondrial function, and actin dynamics. Our study demonstrates the utility of spatial optoproteomics in mapping immune synapse architecture and identifies candidate molecules that influence tumor susceptibility to γδ T cell–mediated cytotoxicity. These insights provide a foundation for optimizing γδ T cell–based immunotherapies against lung cancer.

Title of Project: Novel Approaches for Disrupting KRAS Feedforward Loops in PDAC Treatment
Project No.: NHRI-EX114-11219BI
P.I.: Yuh Pyng Sher/佘玉萍
Key Professional Personnel: Shih-Jen Liu/劉士任, Wei-Chung Cheng/鄭維中, Chun-Chieh Yeh/葉俊杰
Affiliation/Institution: China Medical University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

According to the fact that KRAS mutation diversity and the co-existence of multiple KRAS mutants in the pancreatic tumor, the universal KRAS-targeting would be a promising approach for PDAC treatment. We reveal that a disintegrin and metalloproteinase domain 9 (ADAM9) contributes a feed-forward effect to enhance KRAS activity positively. Notably, the ADAM9 suppression-enhanced KRAS degradation is a universal phenomenon in pancreatic cancer harboring wild-type or mutant KRAS. Intriguingly, we have uncovered that ADAM9 translocates from the membrane into the nucleus, and nuclear ADAM9 operates as a transcriptional repressor to maintain low levels of plasminogen activator inhibitor-1 (PAI-1). We describe endogenous plasminogen activator inhibitor 1 (PAI-1) as a novel selective autophagy receptor that eliminates KRAS proteins under stress. The up-regulated PAI-1 directly interacts with KRAS and LC3 to induce the lysosomal degradation of KRAS under ADAM9-depleted conditions. Notably, developed ADAM9 inhibitors function as pan-KRAS inhibitors across different KRAS mutants and thus have a significant impact on pancreatic cancer treatment. Moreover, we have investigated whether ADAM9 reduction in PDAC cells can reverse the immunosuppressive tumor microenvironment. We proved that ADAM9 reduction indeed decreased the mitochondrial function of pancreatic cancer cells and enhanced the STING signaling in PDAC cells. After ADAM9 inhibitor treatment in syngeneic PDAC mouse models, we showed that the infiltrated CD8 T cells and DC cells were increased. We anticipate that these results elucidate a novel mechanism of immune modulation and offer a promising avenue for improving immunotherapy efficacy in pancreatic cancer.

Title of Project: To Investigate the Role of NUDT16L1 in Ferroptosis Insensitivity During Colon Cancer Progression

Project No.: NHRI-EX114-11220BI

P.I.: shih-chieh Lin/林世杰

Key Professional Personnel: Yi-Syuan Lin/林逸宣, Chia-Jung Li/李佳榮, Bo-Wen Lin/林博文, Shang-Rung Wu/吳尚蓉

Affiliation/Institution: National Cheng Kung University

Entire Project Period: From 2023 to 2025 (Total: 3 years)

The induction of ferroptosis, a regulated iron-dependent form of cell death characterized by lipid peroxidation, has recently gained significant attention as a promising strategy in cancer therapy. However, its clinical translation is hindered by an incomplete understanding of ferroptosis sensitivity across cancer types and the key regulators involved. In this study, we investigate the role of ferroptosis in colorectal cancer and identify NUDT16L1 as a novel ferroptosis suppressor that contributes to ferroptosis insensitivity in this malignancy. Mechanistically, NUDT16L1 promotes ferroptosis insensitivity by directly binding NAD-capped RNAs and indirectly modulating the long non-coding RNA MALAT1, thereby enhancing the expression of mitochondrial and ferroptosis-suppressive genes. Furthermore, NUDT16L1 localizes to mitochondria, where it preserves mitochondrial function and prevents mitochondrial DNA leakage following ferroptosis inducer treatment. Functional studies using orthotopic injection and Nudt16l1 transgenic mouse models confirm the tumor-promoting role of NUDT16L1 in colorectal cancer. Clinical analysis further reveals elevated NUDT16L1 expression in patient tumor samples, underscoring its potential as a therapeutic target. Finally, we demonstrate the efficacy of a NUDT16L1 inhibitor *in vitro*, *in vivo*, and ex vivo, supporting its clinical relevance. Together, our findings uncover a key mechanism of ferroptosis resistance and highlight NUDT16L1 as a promising target for colorectal cancer therapy.

Title of Project: The Role of Cancer-associated Myelopoiesis in Tumor Progression of Bone Metastatic Prostate Cancer and Potential Interventions.

Project No.: NHRI-EX114-11221BI
P.I.: Hui-Ming Chen/陳繪名
Key Professional Personnel: Pei-Wen Hsiao/蕭培文
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Bone metastasis (BnMet) associated with advanced-stage cancer develops a typical so-called “cold” immune landscape. The coincidence of the myelopoiesis skewing and lymphopoiesis impairments in bone microenvironment may hold the keys for constituting “cold” immune landscape tumors and restraining the efficacy of current immunotherapies. Up to date, little is known about whether or how myelopoietic cells in the bone marrow (BM) compartment impact BnMet in the BM.

To address this issue, we first established BnMet tumor cells and compared the transcriptional and proteomic of parental vs BnMet prostate cancer cells. We observed that RM1BnMet tumor cells conferred hypersialylated glycocalyx and upregulated key genes involved in the BnMet and immune regulation, including Bone morphogenetic protein 6 (BMP6), CXCL16, Leupaxin (Lpxn), RANKL and Osteopontin. We observed that myelopoietic progenitors and inflammatory/pro-angiogenetic macrophages highly positively correlated with bone marrow-infiltrating tumor cells. The late stage of tumor expansion status arrested the terminal differentiation of Ly6Chi intermediate progenitors and promoting vigorous myelopoiesis. We identified that Siglec-F could be expressed on particularly myelopoietic progenitors and bone marrow Ly6Chi monocytes in the bone metastatic tissues. The presence of Siglec-F may hinder the repopulating ability of Ly6Chi intermediate progenitors from the bone chimera model. Furthermore, Siglec-Fpos tumor-associated intermediate progenitors have higher active proinflammatory signalings and involved in hematopoiesis regulation. We characterized the scRNA, tumor progression and the immunophenotypical changes in Siglec-FKO vs WT tumor-bearing mice in mouse bone metastatic PCa model. In parallel, we collected the clinical data of 30 primary and 39 BnMet prostate cancer patients from the TCGA and WCDT-MCRPC cohort study. We observed that the high expression of ST3GAL4 tended to predict a worse prognosis in the BnMet patients. ST3GAL4 were remarkable highly expressed in late stage of prostate cancer and myeloma tissues suggested that the sialoglycans signalings could promote tumor progression in BnMet prostate cancer patients.

This study suggests that Siglec-F-sialoglycoprotein axis can be a glycoimmunotherapeutic strategy for reprogramming disease-associated myeloid cells and ameliorating disease progress.

Title of Project: Drug–protein–pathway–disease Deconvolution for Mechanism of Action and Cancer Drug Development

Project No.: NHRI-EX114-11301BI

P.I.: Jinn-Moon Yang/楊進木

Key Professional Personnel: Zi-You Bao/包紫又, Guan-Wei Liao/廖冠維, Jinn-Moon Yang/楊進木

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Drug repurposing offers an efficient alternative to the costly and time-consuming process of de novo drug discovery. However, drug-target-pathway-disease relationships are typically sparse, heterogeneous data integration remains challenging, and deep learning models often lack interpretability, limiting insights into drug mechanisms of action and discovery. We propose a Graph Transformer-Convolutional Network (GTCN) that models drugs, targets, pathways, and diseases as a heterogeneous graph. Graph Transformer Networks (GTNs) address sparsity by strengthening critical edges and inferring missing relationships, while Graph Convolutional Networks (GCNs) refine node feature representation via local subgraph convolution. An attention mechanism highlights important edges and improves interpretability of drug action. GTCN achieves the highest F1-score (0.799), and recall (0.941) on the imbalanced REDDA dataset among comparing nine models. To demonstrate model interpretability and biological relevance, we found that drug-disease edges consistently received the highest attention, reflecting GTCN strongly focus on relevant associations across all experiments. Furthermore, for target therapy Temsirolimus, GTCN identified its known target mTOR and suggested new therapeutic opportunities for breast and lung cancers. Methotrexate (chemotherapy) revealed strong associations with its known target DHFR and identified novel links to thyroid cancer. These findings demonstrate the effectiveness of GTCN in identifying both established and novel biological relationships, highlighting its potential for drug repurposing and applications in precision medicine. The proposed dataset and source code are available at https://github.com/zhengyutong99/GTCN.

Title of Project: Study and Modulation of the Brain Tumor Microenvironment for Brain Disease Therapeutics Development

Project No.: NHRI-EX114-11302BI

P.I.: Kuo-Chen Wei/魏國珍

Key Professional Personnel: Hao-Li Liu/劉浩澧, Hung-Wei Yang/楊閎蔚, Bertrand Chin-Ming Tan/譚賢明, Ko-Ting Chen/陳科廷, Ya-Jui Lin/林亞銳, Chiung-Yin Huang/黃瓊瑩

Affiliation/Institution: Chang Gung Medical Foundation

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Glioblastoma (GBM), the most aggressive subtype of glioma, remains a major clinical challenge due to its poor prognosis, with a median overall survival of approximately 16 months despite standard multimodal therapy. The complex and heterogeneous tumor microenvironment (TME), consisting of neurons, vascular and glial cells, immune components, and other physiological factors, plays a critical role in tumor progression and therapeutic resistance. In this study, we aimed to characterize the cellular composition of glioma tissues and its prognostic implications, while also exploring novel therapeutic strategies.

Utilizing a clinical brain tumor database established with support from the National Health Research Institutes—which includes tumor and blood samples, imaging data, and glioma stem cell cultures—we developed a deconvolution-based analysis of bulk RNA sequencing data to estimate six key cell populations in glioma tissues. Analysis of TCGA and CGGA datasets revealed a positive correlation between tumor cell and endothelial cell abundance, while glioma-associated macrophages and smooth muscle-like cells were inversely associated. Notably, higher endothelial cell content predicted better patient survival, whereas macrophage abundance was linked to poorer outcomes, underscoring the prognostic significance of TME composition.

In parallel, we investigated the efficacy of sonodynamic therapy (SDT) as a non-invasive treatment for brain tumors. Preclinical evaluations of two distinct sonosensitizers demonstrated that sufficient intratumoral accumulation is essential for therapeutic efficacy. However, the blood-brain barrier (BBB) poses a major hurdle, highlighting the need for sonosensitizers capable of BBB penetration and microenvironment-specific targeting.

Together, our findings provide insights into the prognostic relevance of TME components and support the continued development of SDT as a promising treatment strategy. This dual approach—combining cellular profiling with therapeutic innovation—aims to advance precision medicine for malignant brain tumors.

Title of Project: Molecular Mechanisms of Arl4A/D Small GTPases Signaling in Cancer Development

Project No.: NHRI-EX114-11306BI
P.I.: Fang-Jen Lee/李芳仁
Key Professional Personnel: Ting-Wei Chang/張庭瑋, Chia-Tang Chen/陳迦燈
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Activation of extracellular signal-regulated kinases 1 and 2 (Erk1/2) at the plasma membrane usually leads to their translocation to various intracellular sites, where scaffolding proteins mediate substrate targeting. However, in platelet-derived growth factor (PDGF)-induced signaling, Erk1/2 phosphorylate Pak1 to drive cell migration while remaining at the plasma membrane, raising the question of whether scaffolding proteins are required. Similarly, the small GTPase Arf-like protein (Arl4D) promotes cell migration by recruiting Pak1 to the plasma membrane and facilitating its phosphorylation, though the mechanism linking recruitment to phosphorylation remains unclear. To address these questions, we show that Arl4D functions as a scaffolding protein by recruiting Erk1/2 and Pak1 to the plasma membrane, assembling them into a functional complex. This complex allows Erk1/2 to phosphorylate Pak1, supporting its role in cell migration. Our findings identify Arl4D as a novel regulator of Erk1/2, reveal a conserved role of scaffolding proteins in Erk1/2 substrate targeting, and uncover an unrecognized interplay among Arl4D, Erk1/2, and Pak1. These insights provide a deeper understanding of the molecular coordination underlying Pak1-mediated cell migration and its regulation by Erk1/2 and Arl4D.

Title of Project: TEAD4 Drives the Metabolic Plasticity to Induce Therapeutic Resistance of Prostate Cancer Through Epigenetic Remodeling

Project No.: NHRI-EX114-11307BC

P.I.: Chia-Lin Chen/陳嘉霖

Key Professional Personnel: Chia-Lin Chen/陳嘉霖, Sheng-Chieh Hsu/許勝捷, Hsing-Jien Kung/龔行健

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2027 (Total: 4 years)

Castration-resistant prostate cancer (CRPC) is the most aggressive form of prostate cancer, characterized by resistance to standard androgen deprivation therapy and poor patient survival. Our previous work using patient-derived xenograft models revealed TEAD4's critical function in the transition from androgen receptor-positive cluster to neuroendocrine prostate cancer cluster, highlighting its involvement in lineage plasticity. *In vitro*, the knockout of TEAD4 abrogates the development of resistance induced by long-term drug treatment, reinforcing its essential role in promoting lineage transformation. This study aims to explore the role of TEAD4 in promoting therapeutic resistance through the modulation of epigenetic and metabolic pathways.

To investigate how TEAD4 epigenetically mediates therapeutic resistance on a genome-wide scale, we performed ChIP-seq analyses for both histone H3K27 acetylation (H3K27ac) and TEAD4. We observed significant epigenetic changes in resistant cells compared to parental cells, and the knockout of TEAD4 eliminated these alterations, highlighting its crucial role in sustaining the epigenetic modifications of resistant cancer cells. By integrating the analysis of H3K27ac peaks with TEAD4 peaks, we discovered that TEAD4 is associated with metabolic pathways involving lipid and steroid hormone metabolism and the ferroptosis pathway, indicating that its regulation of these metabolic pathways contributes to resistance. Notably, the knockdown of TEAD4 reversed the profiles of metabolic-related genes, underscoring its role in cancer cell survival strategies. Furthermore, we conducted an integrative analysis to comprehensively evaluate the transcriptional regulation of downstream target genes by TEAD4, merging TEAD4 ChIP-seq data, which reveals its genomic binding sites, with RNA-seq data that reflects gene expression changes. Our results indicate that TEAD4 directly regulates genes associated with lipid and steroid hormone pathways in resistant cancer cells. Notably, pathways linked to ferroptosis, a newly recognized non-apoptotic form of cell death, were prominent among the top rankings, drawing considerable interest in cancer research for their contribution to understanding therapeutic resistance mechanisms.

In conclusion, this study elucidates the multifaceted role of TEAD4 in driving therapeutic resistance in prostate cancer, identifying it as a promising therapeutic target. By targeting TEAD4 and its regulatory networks, new treatment strategies may be developed to improve survival outcomes for patients with CRPC. Future studies will further explore the molecular mechanisms governing these interactions, potentially leading to innovative anti-cancer therapies.

Title of Project: Develop Next Generation Dual Specific Modulators Targeting Receptor Tyrosine Kinases

Project No.: NHRI-EX114-11308BC
P.I.: Po-Han Chen/陳伯翰
Key Professional Personnel: Po-Han Chen/陳伯翰
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Receptor tyrosine kinase (RTK) signaling is essential for regulating cell proliferation, and its dysregulation contributes to oncogenesis and a range of human diseases. Aberrant activation of the epidermal growth factor receptor (EGFR), for instance, is frequently observed in lung cancer and remains a major health concern in Taiwan. While RTK inhibitors (RTKi) have advanced targeted cancer therapies, their clinical application is often limited by acquired resistance and off-target effects.

To address these limitations, we are developing new modalities that modulate RTK signaling by either directly recruiting tyrosine phosphatases to the RTK or regulating its downstream partners. Building on our proof-of-concept study, we previously demonstrated that PhosTACs, a new class of bifunctional molecules designed to recruit tyrosine phosphatases, can effectively reduce EGFR phosphorylation. However, this initial system relied on an engineered $FKBP12^{F36V}$-PTPN2 fusion protein in genetically modified cell lines, which limits its translational potential.

Here, we report our recent progress in two directions: the development of a biologic format of PhosTAC, termed togoPhosTAC, and the discovery of small-molecule ligands for PTPN2. The togoPhosTAC system employs a lipid-based nanoparticle delivery method to encapsulate and co-deliver a pre-fused PhosTAC–phosphatase complex. Using recombinant PTPN2, we achieved rapid and effective EGFR dephosphorylation within 2 hours across multiple cell lines, including wild-type HCC827 lung cancer cells. This dephosphorylation also significantly downregulated downstream signaling events, including GAB1, SHC, and AKT phosphorylation.

While biologic togoPhosTAC may benefit diseases associated with phosphatase dysfunction, we are also pursuing small molecules that can systemically modulate PTPN2 activity. We conducted a small-molecule screen of ~8,000 chemically diverse fragments to identify modulators of PTPN2. We identified and validated five putative activators (A1–A5) and six putative inhibitors (I1–I6). Among them, A1 enhanced PTPN2 activity *in vitro* with an EC_{50} of ~10 μM. AlphaFold3 predictions suggest that A1 may bind to the same region occupied by the C-terminal autoinhibitory tail, potentially displacing it and relieving its inhibitory effect. This model is further supported by a reduction in full-length PTPN2 thermal stability upon A1 interaction (ΔTi = –2.1°C) but not in truncated PTPN2 without C-terminal tail (ΔTi = 0.2°C), suggesting partial unfolding of the C-terminal tail. Conversely, I2 inhibited PTPN2 with an IC_{50} of ~1 μM and induced protein destabilization, as indicated by thermal shift assays and increased PTPN2 precipitation upon I2 incubation. Functionally, I2 also enhanced STAT1 phosphorylation following IFN-γ stimulation, mirroring the activity of known PTPN2 inhibitors such as AC484.

Together, our findings present a dual strategy for modulating PTPN2 activity: protein-based delivery via togoPhosTAC and small-molecule tools for pharmacological intervention. Ongoing efforts include co-crystallization of PTPN2 and modulators, cell-based evidence, and structure-activity relationship will be investigated soon to support future therapeutic development.

Title of Project: Deciphering the Mechanistic Link Between PCNA Tyrosine Phosphorylation and Anti-tumor Immunity: Implications for Immuno-oncology Therapy

Project No.: NHRI-EX114-11317BI

P.I.: Shao-Chun Wang/王紹椿

Key Professional Personnel: Chuan-Chun Lee, Wan-Rong Wu, Liang-Chih Liu, Ting-Yi Liao, You-Zhe Lin, Fang-Ying Lin, Yi-Chun Shen, Feng-Chi Chung, Yuan-Liang Wang, Chih-Hao Lu, Wei-Chung Cheng, Wei-Chao Chang, Yi-Chuan Li, Chih-Tung Lin, Chung-Yu Chen, Sheng-Wen Chen, Tsung-Wei Chen, Hsin-An Shih, Steven Lin, I-Wen Chou, Chen-Yuan Lin, Chang-Fang Chiu, Shao-Chun Wang

Affiliation/Institution: China Medical University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Opposing Function of USP5 in MRE11 Endonuclease Activity to Evade Anti-tumor Immunity

Proliferating cancer cells frequently encounter replication stress, which is known to generate abnormal cytosolic DNA and trigger anti-tumor immune responses. Thus, the ability to evade immune surveillance is critical for the development and progression of malignant tumors for which the mechanisms are not fully understood. The MRE11 nuclease, essential for maintaining DNA integrity during cell proliferation, plays important roles in processing stalled replication forks during replication stress. This process produces single-stranded DNA (ssDNA) intermediates which activate the cGAS-STING cascade when released into the cytoplasm to trigger anti-tumor immunity. In this study, we demonstrate that in cancer cells experiencing endogenous replication stress induced by the loss of phosphorylation at tyrosine 211 of the proliferative protein PCNA (pY211-PCNA), MRE11 is modified by site-specific polyubiquitinations. The modifications activate the endonuclease activity of MRE11, favoring cytosolic ssDNA production and subsequent immune response, which sensitizes cells to killing by natural killer (NK) cells. In contrast, in cells expressing pY211-PCNA, the ubiquitin-specific protease USP5 is recruited to replication forks, where it deubiquitinates MRE11, selectively reducing its endonuclease activity, suppressing cytosolic ssDNA generation, and blunting the immune response. Elevated USP5 levels correlate with tumor metastasis and poor prognosis in breast cancer patients. Downregulation of USP5 results in enhanced infiltration of innate and adaptive immune cells and tumor suppression in immune-competent mouse xenograft models, but not in immune-deficient models. Inhibition of USP5 renders patient-derived tumor organoids (PDTOs) susceptible to immune cell-mediated killing. Unbiased screening and biochemical verification identified two FDA-approved drugs as potent USP5 inhibitors. Treatment with these agents phenocopies USP5 downregulation by enhancing cytosolic ssDNA production, increasing sensitivity to killing by NK and T cells, and tumor suppression in syngeneic mouse models. Furthermore, these treatments sensitize PDTOs to cytotoxic killing by NK cells and patient-autologous primary peripheral blood mononuclear cells (PBMCs). This mechanistic insight advances our understanding of tumor progression and the programming of immune responses, potentially leading to novel therapeutic strategies that harness anti-tumor immunity.

Title of Project: Identification of Acalabrutinib's Novel Function and Molecular Action Against PCa Cell Invasion and Metastasis

Project No.: NHRI-EX114-11318BI
P.I.: Ming-Shyue Lee/李明學
Key Professional Personnel: Hsin-Ying Lin/林心瀅
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Metastasis remains the leading cause of cancer-related mortality, underscoring the urgent need for effective therapeutics targeting cancer cell dissemination. The metastatic process relies heavily on dynamic actin cytoskeleton remodeling and enhanced cell motility. In this study, we explored the therapeutic potential of acalabrutinib (ACA), an irreversible Bruton's tyrosine kinase (BTK) inhibitor in prostate cancer (PCa), since BTK has been proposed as a putative therapeutic target. Interestingly, ACA significantly suppressed PCa cell motility with minimal effects on cell proliferation, and this inhibitory effect was found to be independent of BTK expression, suggesting an alternative, BTK-independent mechanism of action. To uncover the underlying target, we employed an antibody-based chemical proteomics approach and identify a novel ACA-binding protein 1, termed ABP-1. Moreover, ACA was found to covalently bind ABP-1 and disrupted its cytoskeleton-regulatory functions, thereby impairing cellular motility. *In vivo* studies further demonstrated that ACA significantly inhibited PCa primary tumor growth and reduced metastatic spread to the lung, liver, and bone in xenografted mouse models. These findings together reveal a previously unrecognized target of ACA in prostate cancer and support its potential repurposing as an anti-metastatic agent in prostate cancer treatment.

Title of Project: Evaluation of Drug Response Using Patient-derived Tumor-microenvironment-on-chip for Breast Cancer

Project No.: NHRI-EX114-11319BI
P.I.: Jen-Huang Huang/黃振煌
NHRI Researcher: Hsin-Ling Hsu/徐欣伶
Key Professional Personnel: Hsuan-Yu Mu/穆宣佑
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Current models for predicting drug responses in breast cancer, including 2D cultures, tumoroids, and animal studies, often fail to reproduce the complexity of the tumor microenvironment (TME), capture intratumoral heterogeneity, or support spatially resolved drug response assessment. These limitations often lead to inaccurate clinical translation. To address these challenges, we developed a three-dimensional dynamic Tumor-Microenvironment-on-Chip (TMoC) platform capable of culturing patient-derived tumor cells and enabling real-time, region-specific drug response evaluation. To validate the platform, we first conducted extensive preclinical studies using tumors derived from mouse models. A total of 15 clinically relevant drugs, including chemotherapy, targeted therapy, immunotherapy, and combination regimens, were tested. The results showed a 93% concordance with outcomes from *in vivo* animal experiments, demonstrating the robustness and predictive power of the TMoC system. We further applied the TMoC to four breast cancer patient-derived tumor samples, collected post-surgery. Through dynamic perfusion culture, the platform allowed real-time, spatially resolved analysis of chemotherapy and combination drug responses. Based on the results, personalized treatment recommendations were proposed, highlighting drugs that demonstrated superior efficacy compared to controls. In cases showing limited response, potential drug resistance was inferred, and alternative therapeutic strategies were suggested. This study is designed as a non-interventional, observational clinical study. All treatment decisions are made independently by physicians. The chip-based data is generated post-operatively and used solely for research purposes. Clinical outcomes—including treatment response, disease-free survival, and adverse effects—are being tracked longitudinally. To support future clinical translation, we are also conducting: (1) genomic comparisons between original tumors and chip-cultured tissues, (2) extracellular matrix analysis, (3) xenograft validation of chip-cultured tumors in immunodeficient mice, and (4) correlation studies comparing chip-based drug response with actual clinical records. While immune cell integration has not yet been implemented in the clinical component, immune-TME modeling has been explored in animal models to assess the feasibility of incorporating immunotherapeutic evaluation into the platform in future studies.

Keywords: tumor-on-a-chip, breast cancer, patient-derived tumor cells, drug screening, tumor microenvironment, precision oncology

Title of Project: Pan-cancer Analysis of Protein Kinase Activity Map Based on Multi-Omics and Single-cell Transcriptomics

Project No.: NHRI-EX114-11320BI

P.I.: Tzong-Yi Lee/李宗夷

Key Professional Personnel: Chia-Ru Chung/鍾佳儒, Yun Tang/唐鈺

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Pancancer Kinase Activity Profiling Reveals Dysregulated Signaling Networks in Tumor Progression

Protein kinases regulate phosphorylation, a key post-translational modification (PTM) critical for protein function, stability, and signaling. Aberrant kinase activity is a hallmark of cancer, driving oncogenic pathways and making kinases promising therapeutic targets. To elucidate kinase dysregulation across cancer types, we developed an integrative framework combining phosphoproteomic profiling, kinase activity inference, network modeling, and clinical association analysis.

We curated and harmonized phosphoproteomic and proteomic datasets from over 45 databases across multiple cancer types. Using a regression-based approach, we inferred kinase activity from substrate phosphorylation data, mapped to curated kinase-substrate relationships. Statistical tests identified dysregulated kinases by comparing tumor versus normal samples. Network visualizations illustrated kinase-substrate interactions and pathway convergence.

The inferred kinase activity profiles revealed cancer-associated kinases with potential functional relevance. In hepatocellular carcinoma (HCC), principal component analysis and clustering distinguished tumors from normal samples. Differential analysis identified upregulated kinase genes including CDK17, ULK1, CAMK1, and PINK1, which are linked to autophagy, stress response, and cell cycle regulation. Mapping these kinases to the kinome tree showed enrichment in CMGC, CAMK, and TK families. Survival analysis revealed that high expression of DAPK2, BRSK1, and CAMK1 correlated with poorer prognosis. Notably, PINK1 showed increased kinase activity without corresponding mRNA changes, highlighting the value of phosphoproteomic data. Across datasets, PKN2 consistently appeared as a tumor-enriched kinase with elevated activity in colorectal (CRC) and lung adenocarcinoma (LUAD), and its substrate network revealed extensive links to oncogenic and tumor-suppressive pathways.

Our framework reveals cancer-specific kinase activity patterns and highlights functionally relevant kinases like PKN2. These findings demonstrate how integrated phosphoproteomic analysis can uncover novel regulatory mechanisms and therapeutic vulnerabilities, providing deeper insights into tumor biology and advancing precision oncology.

Title of Project: Functional Study of DUSP2-regulated CARM1 in Colon Cancer Progression
Project No.: NHRI-EX114-11321BI
P.I.: Shaw-Jenq Sean Tsai/蔡少正
Key Professional Personnel: 傅兆麟
Affiliation/Institution: National Cheng Kung University/National Chung Cheng University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Loss-of-DUSP2-Induced CARM1 Overexpression Contributes to Chemoresistance in Colorectal Cancer

Drug resistance remains a formidable challenge in the treatment of colorectal cancer (CRC), limiting the long-term success of chemotherapy and contributing to disease recurrence and poor prognosis. Despite numerous efforts, the intricate signaling pathways by which cancer cells adapt to survive from chemotherapeutic stress are not yet fully elucidated. In this study, we delineated that dysfunction of dual-specificity phosphatase 2 (DUSP2), a key suppressor of hyperactivated MAPK signaling, promotes drug resistance and cancer progression. Anticancer drug-induced DNA damage triggered the dephosphorylation and functional inactivation of DUSP2. This loss of phosphatase activity resulted in the persistent activation of c-Jun N-terminal kinase (JNK) and subsequent induction of the transcription factor early growth response 1 (EGR1). Importantly, this DUSP2-JNK-EGR1 signaling axis directly enhances the transcription of coactivator-associated arginine methyltransferase 1 (CARM1), a transcriptional coactivator and epigenetic regulator implicated in tumorigenesis. Single-cell RNA sequencing and immunohistochemical analyses of human CRC specimens revealed that CARM1 was significantly overexpressed in tumor tissues compared to adjacent normal tissues, with elevated expression correlating with advanced disease stage and poor patient survival. Functional studies confirmed that pharmacological inhibition or genetic ablation of CARM1 effectively restored chemosensitivity, reduced cellular proliferation and invasiveness, and suppressed tumor growth in both *in vitro* assays and an orthotopic CRC mouse model. Furthermore, comparative analysis between parental and drug-resistant CRC cell lines indicated that reduced DUSP2 expression is a driving factor behind CARM1 overexpression in resistant clones. Notably, CARM1 inhibition sensitized drug-refractory cancer cells to chemotherapy. Clinically, high CARM1 expression was strongly associated with inferior outcomes among CRC patients receiving adjuvant chemotherapy, suggesting that chemotherapy-induced inactivation of DUSP2 may lead to CARM1-driven resistance. These findings established a novel mechanistic link between the DNA damage response and oncogenic reprogramming in CRC, mediated by the DUSP2-JNK-EGR1-CARM1 axis. Our study highlights CARM1 as a pivotal effector in CRC chemoresistance and a promising target for therapeutic intervention aimed at overcoming treatment failure and improving long-term patient survival.

Title of Project: KIF2C as a Novel Therapeutic Target of Breast Cancer
Project No.: NHRI-EX113-11124BI
P.I.: Lily Hui-Ching Wang/王慧菁
NHRI Researcher: Ching-Chuan Kuo/郭靜娟
Key Professional Personnel: Lily Hui-Ching Wang/王慧菁, Ching-Chuan Kuo/郭靜娟
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2022 to 2024 (Total: 3 years)

In this project, we addressed the issue of chemotherapy resistance in cancer treatment, with a focus on triple-negative breast cancer (TNBC), a breast cancer subtype prone to recurrence and multidrug resistance. The study identifies Kinesin family member 2C (KIF2C), a microtubule (MT) depolymerase essential for maintaining genomic stability during cell division, as being overexpressed in paclitaxel-resistant TNBC cells. This overexpression enables cancer cells to bypass the cytotoxic effects of paclitaxel and sustain proliferation. Mechanistically, chemoresistant cells augment KIF2C's depolymerizing activity through tubulin polyglutamylation, enhancing KIF2C-tubulin interactions and facilitating MT disassembly. To combat this resistance, our research team developed 7S9, the first-in-class small-molecule inhibitor of KIF2C, possessing excellent cell permeability and high specificity. 7S9 disrupts KIF2C's function by intercalating into the KIF2C-tubulin complex, blocking the conformational changes required for its release and microtubule depolymerization. Preclinical studies reveal that combining 7S9 with paclitaxel yields strong synergistic anti-tumor effects, reversing resistance not only to paclitaxel but also to other microtubule-targeting agents. Additionally, cytoplasmic KIF2C expression correlates with lymph node metastasis and tumor progression, highlighting its potential as a biomarker for breast cancer. In the future, we aim to advance 7S9 into preclinical development, offering promising therapeutic prospects for TNBC and potentially gynecological tumors that exhibit elevated KIF2C expression and a poor prognosis.

Title: The HDAC Inhibitor Synergistically Enhances the Anti-tumor Efficacy of PD-1 Inhibitor Therapy in the Treatment of Colorectal Cancer

P.I.: Jen-Yang Chen/陳振陽
Presenter : Mei-Shu Chen/陳玫束
Institute/Center : National Health Research Institutes

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide, characterized by uncontrolled cell growth in the colon or rectum. Despite advances in treatment, immune checkpoint inhibitors, such as programmed cell death protein-1 (PD-1) inhibitors, have shown limited efficacy as monotherapies in CRC, particularly in microsatellite stable (MSS) tumors, due to immunosuppressive tumor microenvironments and low tumor immunogenicity. Histone deacetylase (HDAC) inhibitors, which modulate gene expression by altering chromatin structure, have emerged as promising anticancer agents. These inhibitors can induce tumor cell apoptosis, inhibit proliferation, and enhance immune recognition by upregulating tumor-associated antigens and MHC molecules. By leveraging the immunomodulatory effects of HDAC inhibitors to reshape the tumor microenvironment, we hypothesize that combining an HDAC inhibitor with a PD-1 inhibitor may enhance anti-tumor efficacy in the treatment of CRC.

We tested HDAC inhibitor X with/without PD-1 antibody-Nivolumab in the HT-29 cell line, a cell line derived from a primary tumor obtained from a 44-year-old white female patient with colorectal adenocarcinoma, for 24 hr. The results showed that the combination treatment of HDAC inhibitor X and Nivolumab displays a significant cell-killing efficacy *in vitro*. Moreover, we established a hu-PBMC mouse model to assess the therapeutic efficacy of the treatment with HDAC inhibitor X and/or Nivolumab in advanced severe immunodeficiency (NPG) mice. The HDAC inhibitor X, combined with Nivolumab, demonstrated a significant enhancement in anti-tumor effect in an HT-29 xenograft hu-PBMC mouse model.

In conclusion, the combination treatment of HDAC inhibitor X and Nivolumab significantly enhances the therapeutic efficacy on colorectal cancers, exhibiting great potential for colorectal cancer therapy.

Title of Project: CAP-resin-rhTM As Sustained Release Bone Cement for the Stimulation of Spinal Fusion in Intervertebral Disc of Rat Tail Model
Project No.: NHRI-EX114-11113EC
P.I.: Yan-Jye Shyong/熊彥傑
Key Professional Personnel: Cheng-Li Lin/林政立
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

3D Printing Intervertebral Cage with Simvastatin Loading to Increase Cage Stability and Promote Intervertebral Disc Fusion

A major challenge during interbody fusion through orthopedic surgery is cage subsidence and scatter of the implant. This is caused by the instability of the implant as motion may occurs during post-surgical recovery. This study aims to enhance implant stability and fusion efficiency using a comprehensive approach. The primary objective involves the development of a customized 3D printing polyethylene glycol diacrylate (PEGDA) cage, based on preoperative CT imaging, which will perfectly fit into the intervertebral disc space. Cage will feature barb surface structures for increased friction, promoting early-stage implant stability. Subsequently, a mesh-like porous structure will be established in the cage, enable cell growth and facilitate fusion between the adjacent vertebrae. To further enhance interbody fusion, simvastatin (SIM) will be printed into the cage during synthesis. By utilizing the non-thermal characteristic of stereolithography (SLA) 3D Printing technic, which will allow SIM to be fully dispersed into the resin matrix without degradation. The printed cage will directly contain SIM, which can stimulate and guide newly grown bone cells from endplate into the mesh structure of the cage, further providing lone term stability to the implant. We also incorporated SIM into the developed calcium phosphate (CaP) microparticle graft, to stimulate solid bone generation in disc region, enhancing the efficacy of interbody fusion of CaP, compellable to gold standard allograft bone used in clinical practice. The slow biodegradable nature of cage and CaP graft will ensure sustained drug release, addressing the limitations of single-dose administration during long-term fusion period. We believe our study design can enhance implant stability and promote effective interbody fusion for improved treatment outcomes.

Title of Project: Deep Learning-enhanced Ultra-low-count Tau PET Neuroimaging
Project No.: NHRI-EX114-11205EC
P.I.: Kevin Tze-Hsiang Chen/程子翔
Key Professional Personnel: Kevin Tze-Hsiang Chen/程子翔
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2026 (Total: 4 years)

Consistency Model-enhanced Low-count Tau PET Neuroimaging

Deep-learning methods can be used for low-count PET enhancement to reduce scan times and/or radiation exposure of PET exams while maintaining image quality. Recently, tau PET imaging has been employed to assess Alzheimer's disease (AD) and tau pathology *in vivo*. Nevertheless, research on the enhancement of low-count tau PET remains understudied. Given the oversmoothed textures and limited reliability of traditional deterministic models, in this study, we aim to enhance low-count tau PET images by using a conditional consistency model (cCM) and a novel multi-frame generation process. The cCM generates a specified number of low-count-like images based on the PET dose reduction factor (DRF), synthesized into enhanced images. The method was evaluated on datasets with DRFs of 3 and 6, showing a consistent result.

The cCM was adapted from consistency models, a class of generative models designed to map random noise to data in a single step, more efficient than diffusion models. During inference, the enhanced images were synthesized with multiple low-count-like PETs generated from Gaussian noise by cCM. To assess the impact of the strategy, low-count PET datasets with dose reduction factors (DRF) of 3 and 6 were implemented for zero-shot and normal inference, respectively. 46 participants (26 female, 2 unknown; 66.89±9.52 years), of which 6 were scanned twice, were recruited to train the ultra-low-dose tau network; the participants included individuals with a range of neurodegenerative disorders as well as healthy controls. 274±82 MBq of the tau radiotracer [^{18}F]-APN-1607 was injected. Static PET data, subdivided into 6 5-minute subframes, was acquired 90-120 minutes post-injection. In this study, the first frame was defined as DRF-6 low-count PET (LPET), while the ground truth was defined as the mean of the six frames. In addition, a DRF-3 LPET dataset was created by averaging two adjacent frames and reserved for zero-shot inference. All models were trained using 2.5-D and multimodal inputs, with six-fold cross-validation stratified by clinical diagnosis, scanner type, and reconstruction protocol. UNet3+ models were trained as representative traditional deterministic models for comparison purposes.

Upon visual inspection, compared with the image texture of the DRF-6 LPETs and U-Net-enhanced PETs, the former was noisier and the latter was smoother than that of our method. Images enhanced by multi-frame generation can achieve a texture more similar to the ground truth. To quantitatively assess the similarity between our enhanced images and ground truth, normalized mean square error (NMSE), peak signal-to-noise ratio (PSNR), and structural similarity (SSIM) were evaluated. Statistical analysis showed that our method significantly outperforms the baseline in all metrics and is comparable to the results of the U-Net-based model. The zero-shot inference on the DRF-3 dataset demonstrated the consistent generative performance and the generalizability of the cCM, outperforming the deterministic model and representing the importance of the conditioning strategy. We also showed that using more generated frames results in better quality of the enhanced images. Furthermore, conditioning on DRF-3 images yields an image quality comparable to that of the DRF-6 condition when using twice as many frames, indicating that cCM can reflect the DRFs of the conditional images on the generated low-count-like images.

Title of Project: Immunofoam: an Innovation for Intracavitary Combination Therapy to Solid Tumors Using Biomaterials-assisted Immunotherapy and Sonoporation-enhanced Drug Penetration

Project No.: NHRI-EX114-11206EC
P.I.: Yen-Liang Liu/劉彥良
Key Professional Personnel: Ulziijargal Sukhbat, Chin-Yi Yeh/葉沁怡
Affiliation/Institution: China Medical University
Entire Project Period: From 2023 to 2026 (Total: 4 years)

Ovarian cancer (OC) is a formidable adversary in women's health. OC is often diagnosed at advanced stages with pervasive metastasis, necessitating innovative therapeutic paradigms. Here, we aim to develop ultrasound-assisted chemotherapy for treating OC-associated peritoneal metastasis. We have developed an ultrasound-responsive liquid foam that can serve as a drug carrier and perform sonoporation to enhance drug penetration into deep tumors. The foam formulation enables drug carriers to conform to the tissue surface and immerse the cancer cells in therapeutic agents, extending the drug contact time. Ultrasound-responsive microbubbles can further enhance drug penetration through ultrasound-triggered sonoporation. We evaluated the sonoporation using variable ultrasound intensity and duration, and the sonoporation efficacy is proportional to the ultrasound intensity and treatment duration. The cytotoxicity (IC50) of cisplatin and carboplatin to ID8 ovarian cancer cell line was improved more than 100 folds using foam with ultrasound treatment. Our preliminary results in the metastatic ovarian mouse model demonstrated that the foam-carried chemo drugs can penetrate tumors with a depth of 200 μm and achieve better progression after treatment, highlighting the potential for improved treatment outcomes. The therapeutic efficacy was demonstrate in two intracavitary cancer models: ID8 ovarian cancer and LLC lung cancer. The combination of cisplatin-loaded foam and ultrasound treatment significantly prolonged the survival of mice. Immunofoam, ultrasound-assisted intraperitoneal chemotherapy, addresses the current limitations in peritoneal metastasis management and presents a paradigm shift by optimizing therapeutic efficacy while minimizing systemic toxicity. We envision that our approach is promising to improve patient prognosis and contribute substantially to the evolution of precision medicine in OC management. Evaluate the efficacy of ultrasound-enhanced chemotherapy in enhancing drug penetration and cytotoxicity *in vivo*.

Title of Project: Translational Investigation of Very Low Intensity Ultrasound on the Treatment of Degenerated Intervertebral Disc
Project No.: NHRI-EX114-11222EI
P.I.: Jaw-Lin Wang/王兆麟
Key Professional Personnel: Guan-Jen Chen/陳冠蓁, Chih-Ping Chang/張芷蘋
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Effects of Rigid PZT and Flexible PVDF Piezoelectric Probes on Extracellular Matrix and Inflammatory Response in Degenerated Intervertebral Discs

[Introduction] Low back pain (LBP) is a major global health issue, often caused by intervertebral disc degeneration (IDD). The disc consists of the nucleus pulposus (NP), annulus fibrosus (AF), and cartilage endplates (EP). IDD, driven by aging and mechanical stress, leads to cell senescence, extracellular matrix (ECM) degradation, and increased inflammatory cytokines such as TNF-α and IL-1β. Intervertebral discs also possess piezoelectric properties, allowing mechanical stimulation to modulate cell behavior and repair. This study explores whether low-intensity pulsed ultrasound (LIPUS) can improve degenerated discs in a mouse model.

[Materials and Methods] A mouse tail looping model was used to induce disc degeneration. LIPUS was applied using piezoelectric materials (PZT and PVDF) to stimulate the discs. ECM proteins (Aggrecan, Collagen I, II) secreted by NP cells were analyzed by Western blot, while IL-1β and TNF-α expression were evaluated using immunohistochemistry (IHC).

[Results] Tail looping successfully induced disc degeneration. LIPUS treatment reduced inflammation and slightly restored ECM protein levels. Among the materials, PVDF outperformed PZT in therapeutic effects. However, while improvement was evident, full recovery of disc structure was not achieved.

[Discussion] LIPUS, particularly via PVDF stimulation, showed promising effects on degenerative discs. These findings support future development of minimally invasive devices for human disc treatment. Further research is needed to optimize parameters and ensure safety for clinical use.

[Conclusions] LIPUS with PVDF stimulation enhances disc repair in a degeneration model, offering potential for non-invasive treatment due to PVDF's favorable biocompatibility and efficiency

Title of Project: Targeting Tissue Stiffness in Radiotherapy: Deciphering the Mechanism and Developing Treatment Strategies
Project No.: NHRI-EX114-11223EI
P.I.: Po-Ling Kuo/郭柏齡
Key Professional Personnel: Jeng-Jong Hwang/黃正仲, Shao-Lun Lu/呂紹綸
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Shear-Wave Elasticity Imaging and 3-D CyTOF Profiling Reveals Matrix Stiffness Modulating Tumor Response to Single-Fraction Radiotherapy in Millimeter-Sized 3D Culture and Dual Murine Models

Background: The mechanical properties of the tumor micro-environment are increasingly recognized as modifiers of radio-response. We therefore combined a stiffness-graded three-dimensional (3-D) culture proteomics screen with two murine irradiation models—a tunable hind-limb xenograft and an orthotopic hepatocellular-carcinoma (HCC) growing in CCl_4-induced cirrhotic liver—to delineate mechanical and molecular determinants of single-fraction radiotherapy.

Methods: 3-D culture. Huh7 cells were embedded in Matrigel/collagen matrices adjusted to match the normal liver stiffness with a shear modulus of 1.5 kPa. Constructs received 16 Gy or sham irradiation and were dissociated 24 h later. Single-cell mass-cytometry (CyTOF, 38-marker panel) profiled DDR and ECM-remodelling pathways. *Ectopic model.* 5×10^6 Hepa1-6 cells were injected sub-cutaneously into nude-mouse hind limbs within soft, medium or stiff hydrogels and treated with a single 20 Gy beam when tumors reached ~6 mm. Caliper volumes and power Doppler ultrasound were recorded at baseline and day 7. *Orthotopic model.* Male C57BL/6 mice received intraperitoneal CCl_4 (0.375 µl g^{-1} × 2 weeks or 0.5 µl g^{-1} × 5 weeks), doubling liver shear modulus. One week later, 5×10^5 Hepa1-6 cells were injected under ultrasound guidance into the left-lobe capsule. A 20 Gy, 10-mm field was delivered on day 7; B-mode ultrasound, shear-wave elastography (SWE) and Doppler imaging were followed to day 21.

Results: 3-D culture. Irradiation produced a uniform increase in DDR proteins (↑pATM, ↑γH2AX) and a reduction in lysyl-oxidase (LOX), indicating acute suppression of collagen cross-linking machinery. Hind-limb xenografts. Non-irradiated controls expanded 19.7-fold in 7 days. A single 20 Gy reduced growth to 11.6-, 11.7- and 12.6-fold in soft, medium and stiff matrices, respectively (growth suppression 41 %, 40 % and 36 %). Doppler imaging demonstrated near-complete loss of intra-tumoral flow after irradiation. Orthotopic HCC. Baseline liver–tumor composite stiffness measured 3.1 ± 0.4 kPa. Twenty-Gy limited largest-axis growth to 1.44-fold by day 14 (~55 % inhibition), while local stiffness rose to 6.2 ± 0.7 kPa and Doppler flow declined; radio-response was similar for both CCl_4 regimens once a ≥2-fold stiffness threshold was reached.

Conclusions: Proteomic fingerprints of mechanotransduction from 3-D culture predict in-vivo radio-response and identify targets such as LOX inhibition to address residual resistance. Doppler imaging shows concomitant vascular rarefaction, and SWE reveals post-irradiation stiffening, suggesting that extracellular-matrix remodeling plus reduced perfusion jointly drive tumor persistence. Larger cohorts integrating CyTOF, SWE and Doppler endpoints are warranted.

Title of Project: Evaluation of Chondrogenesis and Cartilage Repair via Second Harmonic Generation Imaging

Project No.: NHRI-EX114-11224EI

P.I.: Chung-Hwan Chen/陳崇桓

Key Professional Personnel: Shean-Jen Chen/陳顯禎, Chi-Hsiang Lien/連啓翔, Chun-Yu Lin/林俊佑

Affiliation/Institution: Kaohsiung Medical University

Entire Project Period: From 2023 to 2025 (Total: 3 years)

Background: Cartilage repair is a biologically intricate process, particularly due to the avascular nature of articular cartilage and its limited population of stem/progenitor cells. The repair mechanism involves cellular migration and extracellular matrix (ECM) deposition, composed primarily of proteoglycans, collagen, and water. Native cartilage comprises hyaline cartilage rich in type II collagen, while regenerated tissue often results in fibrous cartilage containing type I collagen. However, due to the complex assembly of collagen fibrils, accurate identification and quantification of fibrillar collagen without biomarkers remains a clinical challenge. Currently available clinical evaluation tools such as arthroscopy and MRI are limited in their ability to characterize the composition of the repaired cartilage. Arthroscopy offers only superficial visualization, and MRI lacks molecular specificity. To overcome these limitations, this project aims to develop an intelligent, polarization-resolved imaging system for the quantitative evaluation of collagen remodeling during cartilage repair.

Research approach and Results: Here, we have developed motion-free polarization control for SHG microscopy (PSHG) by utilizing a liquid crystal modulator (LCM) in the infinity space. Purified type I and type II collagen gels, as well as gradient mixtures, are analyzed to quantify peptide pitch angle (PA) and anisotropy parameter (AP) distributions. Additionally, a deep learning model is developed using curated SHG datasets. The PSHG system is applied to porcine cartilage explants and hydrogel-ADSC constructs to monitor regeneration. Comparative validation is conducted using SHG metrics alongside immunohistochemistry (IHC) analysis. Cartilage repair is assessed in animal models including rabbits. HA-based hydrogel scaffolds embedded with ADSCs are implanted, and monitoring of collagen composition is conducted using AI-enhanced PSHG analysis. The outcome holds strong potential for clinical translation and commercialization as a diagnostic tool for evaluating articular cartilage regeneration. Pixel-wise analysis of peptide pitch angle (PA) revealed distinct distributions: the average PA for Col I was 49.73°, while Col II exhibited a significantly higher average PA of 51.59°. These findings confirm that PSHG imaging can differentiate collagen types based on submicron structural differences. In addition, the system successfully captured changes in the regenerated cartilage matrix in ADSC-treated porcine models. For example, regenerated regions showed PA values approaching 51.19°, closer to native hyaline cartilage, suggesting successful remodeling toward Col II dominance.

Title of Project: 3-d Human Pancreatic Lesion Analysis: Duct, Islet, and Neurolymphatic Alterations in Inflammation
Project No.: NHRI-EX114-11225EI
P.I.: Shiue-Cheng Tang/湯學成
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

The pancreas consists of both the exocrine acini and ducts (epithelium) and endocrine islets to facilitate and regulate digestive and metabolic activities. In humans, the acini, ducts, and islets hold direct contacts and form indirect neurovascular association to integrate the pancreatic structures and functions (*note*: unlike human islets, rodent islets are peri-lobular and enclosed by a glial sheath). Because the secretions of digestive enzymes and endocrine hormones are regulated by neuro-vascular signals, morphological assessment of human pancreases should include both the exocrine and endocrine components with neurovascular association to investigate the lobular structures in health and disease (e.g., diabetes or lesion formation). However, due to the dispersed and scattered nature of neurovascular tissues and islets, the clinical 2D histology cannot provide a global and integrated view to analyze the pancreatic tissue network in a 3D space continuum.

In this presentation, we will discuss our recent success of using the high-refractive-index (high-*n*) acrylamide-based polymer for human pancreas embedding and clearing to achieve antifade 3D/Airyscan super-resolution imaging (human liver as a parallel control to evaluate and avoid false positive and false negative results). In addition, we have integrated stereomicroscopy, clinical H&E histology, and in-depth super-resolution imaging to detect, confirm, and characterize the early and local remodeling of human pancreas (e.g., cystic change and low-grade duct lesion). We will use the unique duct-β-cell cluster as an example to illustrate the multimodal, multidimensional, and multiscale approaches of human pancreas imaging in the high-*n* polymer.

Recent publications on multimodal 3D/super-resolution human pancreas and liver histology

1. Lee CY, Kuo TC, Chou YH, Peng SJ, Hsiao FT, Chung MH, Lo LW, Shen CN, Chien HJ, Chang HP, Chen CC, Jeng YM, Tien YW*, **Tang SC***. 3D imaging resolves human pancreatic duct-beta-cell clusters during cystic change. *Diabetes*, 74:734-748, 2025. Official journal of American Diabetes Association (ADA).
   Accompanied by a commentary: "Bend It Like Occam: Ductal Origin of New Islet Cells in Human Pancreas After Injury." Diabetes, 74:682-684, 2025. https://pubmed.ncbi.nlm.nih.gov/40258166/
2. Chen CC, Peng SJ, Chou YH, Lee CY, Lee PH, Hu RH, Ho MC, Chung MH, Hsiao FT, Tien YW, **Tang SC***. Human liver afferent and efferent nerves revealed by 3-D/Airyscan super-resolution imaging. *American Journal of Physiology - Endocrinology & Metabolism*, 326:E107-E123, 2024. American Physiological Society Journal. Cover image on February issue.
3. Hsiao FT, Chien HJ, Chou YH, Peng SJ, Huang TH, Lo LW, Sheng CN, Chang HP, Lee CY, Chen CC, Jeng YM, Tien YW, **Tang SC***. Transparent tissue in solid state for solvent-free and antifade 3D imaging. *Nature Communications*, 14:3395, 2023.
   Highlight: In this paper, we use lesions in the human pancreas to illustrate 3D/Airyscan super-resolution imaging of tissue remodeling in a clinically related setting.
4. Chung MH, Chien HJ, Peng SJ, Chou YH, Chiang TC, Chang HP, Lee CY, Chen CC, Jeng YM, Tien YW*, **Tang SC***. Multimodal 3-D/2-D human islet and duct imaging in exocrine and endocrine lesion environment: associated pancreas tissue remodeling. *American Journal of Physiology - Endocrinology & Metabolism*, 323:E354-E365, 2022. American Physiological Society Journal. Cover image on October issue.

Title of Project: Development of a Modular Four-Way Junction RNAi Scaffold Automatic Production and Packaging System for Targeted Multi-gene Silencing and Immune Checkpoint Blockade Therapy in Breast Cancer

Project No.: NHRI-EX114-11226EI
P.I.: Hung-Wei Yang/楊閎蔚
Key Professional Personnel: Dr. Hao-Han Pang/龐浩翰, Dr. Ying-Tzu Chen/陳映慈
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

This study aims to develop a multifunctional platform for multi-RNA interference (RNAi) and immune therapy targeting TNBC. Based on the achievements of the previous two years, we have successfully established a scalable production process for Fc@4WJ-VLPs and demonstrated stable conjugation with anti-PD-L1 antibodies ($Ab_{PD\text{-}L1}$) to yield the final product, $Ab_{PD\text{-}L1}$@4WJ-VLPs. Comprehensive analyses—including physicochemical characterization, structural identification, cytotoxicity testing, and gene silencing efficiency evaluation—have been completed. Therefore, the current year's project will further focus on validating the therapeutic efficacy of this system through animal studies. As shown in **Figure 1A–C**, treatment with 4WJ-VLPs and $Ab_{PD\text{-}L1}$@4WJ-VLPs significantly suppressed tumor growth compared to the control, VLPs, and $Ab_{PD\text{-}L1}$@4WJ-VLPs groups. Among them, the $Ab_{PD\text{-}L1}$@4WJ-VLPs group exhibited the most potent tumor-inhibitory effect, with markedly reduced tumor volumes observed by Day 25. Notably, all treatment groups maintained stable body weights, indicating minimal systemic toxicity. Immunohistochemical staining for CD3 (**Figure 1D**) revealed enhanced T-cell infiltration in the $Ab_{PD\text{-}L1}$@VLPs group as early as Sac. D1, with further accumulation by Sac. D5, suggesting effective immune activation within the tumor microenvironment. In contrast, no T-cell infiltration was observed in the control and VLPs groups. These findings indicate that $Ab_{PD\text{-}L1}$-integrated 4WJ-VLPs can not only suppress tumor progression but also promote robust antitumor immune responses.

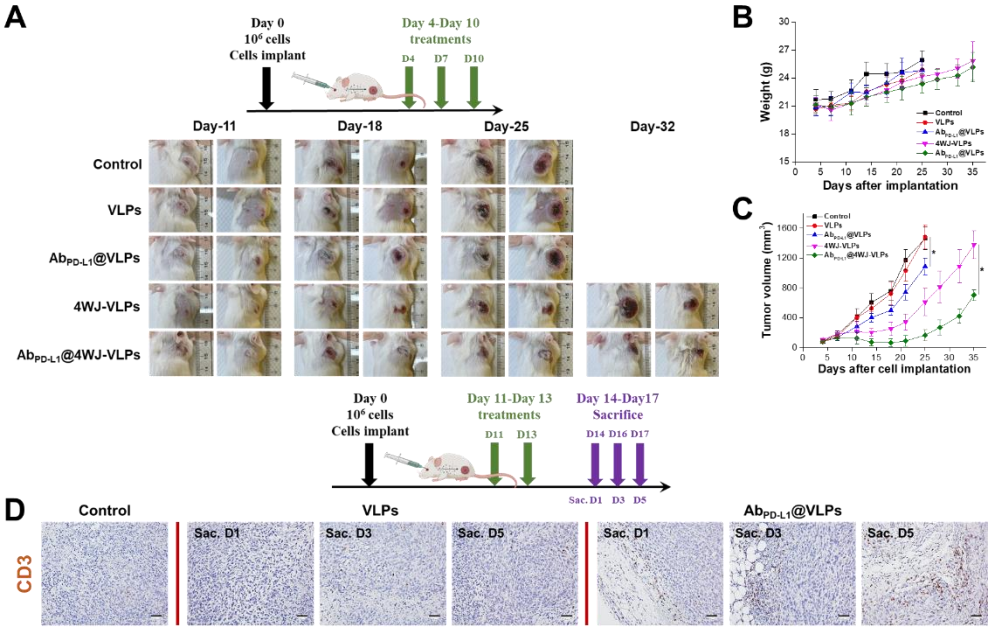


Figure 1. (A) Representative tumor progression images in BALB/c mice bearing 4T1 tumors treated with VLPs, $Ab_{PD\text{-}L1}$@VLPs, 4WJ-VLPs, or $Ab_{PD\text{-}L1}$@4WJ-VLPs on Days 4, 7, and 10 after 4T1 cell implantation. (B) Body weight changes of mice during the treatment period. (C) Tumor growth curves show significant tumor suppression in $Ab_{PD\text{-}L1}$@4WJ-VLPs. Values are expressed as the means ± SDs (n = 8; *p < 0.05). (D) Immunohistochemical staining for CD3 in tumor sections on Sac. D1, D3, and D5 reveal increased T cell infiltration in the $Ab_{PD\text{-}L1}$@VLPs group.

Title of Project: Novel Evaluation of Vestibular Functions for Clients with Cervicogenic Dizziness
Project No.: NHRI-EX114-11227EI
P.I.: Lan-Yuen Timothy Guo/郭藍遠
Key Professional Personnel: Chen-Wen Yen/嚴成文, Chen-Yu Chien/簡禎佑, Lih-Jiun Liaw/廖麗君, Pei-Yun Lee/李佩紜,Chia-Chi Yang/楊家琪, Chin-I Huang/黃勤鎰, Min Hsu/徐敏, Syiar Aprilla Tanazza, Muhammad Uzair Latif
Affiliation/Institution: Kaohsiung Medical University
Entire Project Period: From 2023 to 2025 (Total: 3 years)

Introduction: Cervical Dizziness (CD) is a controversial clinical syndrome often attributed to impaired sensorimotor integration, particularly involving cervical proprioception, which can lead to dizziness. However, not all individuals with neck pain experience dizziness symptoms, which makes diagnosis more difficult. Cervical afferents and vestibular signals influence oculomotor control. The Smooth Pursuit Neck Torsion Test (SPNT) and gain values were used to assess these mechanisms across the neck postures in the yaw axis. Nevertheless, gain alone reflects the matching of movement velocity but does not fully represent the quality or stability of tracking. Therefore, this study aims to develop a comprehensive assessment protocol that incorporates multi-axis proprioception and oculomotor parameters by examining three-dimensional neck joint positioning and smooth pursuit performance across the yaw, pitch, and roll axes better to characterize sensorimotor integration deficits in individuals with neck pain. **Method**: Participants were divided into a neck pain group (VAS > 2 at the upper cervical region) and a control group (VAS $\leq$ 2). Assessments included visual fitness, pain evaluation, Neck Disability Index (NDI), Dizziness Handicap Inventory (DHI), cervical range of motion, and cervicovertebral angle(CVA). Three-axis Joint Position Error (JPE) tests were conducted in seated posture. Eye movement performance was evaluated using a Stewart platform during smooth pursuit tasks across yaw, pitch, and roll axes. Parameters included the gain, angular error, latency, cross-correlation (Xcorr), lag, and SPNT differences. Mann-Whitney U tests were applied due to the non-normal distribution of the data. Logistic regression was used to predict group classification. **Result**: Twelve participants were assigned to the neck pain group and twenty to the control group. Aside from pain intensity, no significant differences were observed in baseline characteristics, including age and cervical mobility. JPE performance showed no significant between-group differences. For oculomotor parameters, no significant group differences were found in gain values across cervical postures (neck pain: 0.55~0.78; control: 0.55~0.63; all $p > 0.10$). However, the gain stability in cervical extension(E) was significantly lower in the neck pain group (median 0.59, IQR 0.57~0.71) compared to controls (0.77, IQR 0.62~1.00; Z = –2.647, p = 0.008). Regarding tracking accuracy, the angular error in left lateral flexion(LLF) was significantly greater in the neck pain group (median 11.47°, IQR 4.81~15.67) than in controls (7.26°, IQR 4.25~9.74; Z = –2.335, p = 0.020). Similarly, angular error stability in extension was lower in the neck pain group (1.57, IQR 1.39~1.86) than in controls (1.41, IQR 1.05~1.50; Z = –2.530, p = 0.011). No group differences were noted in Xcorr or lag overall, but latency in right lateral flexion was longer in the neck pain group (Z = –1.990, p =0.046). SPNT results revealed a significantly higher gain difference in the roll axis in the neck pain group (0.27, IQR 0.15~0.41) compared to controls (0.09, IQR 0.05~0.24; Z = –1.967, p = .049). Logistic regression analysis included five predictors: gain in extension(E) , angular error in left lateral flexion (LLF), lag in E and LLF, and angular error stability in E. The model was significant ($\chi^2(5) = 20.76$, p =0.001), with a Nagelkerke R^2 of 0.650. Among these, lag (E, LLF) and angular error stability (E) were significant predictors ($p < 0.05$), with odds ratios ranging from 193.4 to 416.5. The model demonstrated good fit (Hosmer-Lemeshow p =0.982) and an overall classification accuracy of 84.4%. **Conclusion**: These findings indicate that measuring latency and stability in eye movement tracking across various neck positions could help identify individuals with neck pain. Combining multi-axis performance metrics offers a more complete evaluation of cervical sensorimotor function.

Title of Project: Exploring the Neural Inhibition Hypothesis in Negative Bold Phenomenon.
Project No.: NHRI-EX114-11322EI
P.I.: Jyh-Horng Chen/陳志宏
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Functional magnetic resonance imaging (fMRI) is a non-invasive MRI technique that utilizes the blood oxygenation-level dependent (BOLD) mechanism to measure the changes in blood oxygen concentration. It discovers the function of the brain and widely applies in neuroscience. Current researchers can explain the positive BOLD response (PBR) mechanism with the neurovascular coupling principle. However, the cause of the negative BOLD response (NBR) is still unclear because the fMRI phenomena regarding NBR observed in the past cannot be fully explained by the three hypotheses, which are (1) the vascular hypotheses “the blood stealing” (2) the mix hypotheses “mismatch of hemodynamic response function and neural activity” (3) the neural hypothesis “the neural inhibition.” All three hypotheses have their physiological basis and evidence, so the mechanism of NBR remains a mystery. This project explored the NBR by applying several neueral techniques, functional quantitative susceptibility mapping (fQSM) magnetoencephalography (MEG), and MRS (MR spectroscopy) to quantify the changes in blood oxygen concentration and nerves in the default mode network (DMN) region which is usually observed the negative BOLD response during complex cognitive tasks. 18 healthy participants were recruited and they completed a 2-back working memory task during fMRI imaging. The participants also performed the MEG experiment adapting the same 2 back task to induce brain neural activation. Brain signal were recorded and analyzed using time frequency analysis and source analysis to generate time-frequency response and band power map. The NBR hypotheses were explored by using the frequency band power change with the characteristics of neural excitation or inhibition. To fuse the fQSM and MEG data, we established the ROI in the peak value of fMRI activation area. The susceptibility change and band power change in the ROI were selected to calculate Pearson correlation in 18 subjects. And we also evaluated the similarity between fQSM activation map and MEG band power map using the cosine similarity evaluation.

In the correlation analysis, the susceptibility change in NBR observed in the precuneus of DMN is positively correlated with alpha power ($r=0.51$, $p=0.04$), and the highest cosine similarity compared with other band power also observed in the region. The results indicated that the NBR in precuneus may be related to the neural inhibition hypothesis. It suppressed the irrelevant information, so that the brain can focus on memory tasks.

In summary, this study applied fQSM and MEG to explore the NBR mechanism and provided preliminary evidence for the neural inhibition hypothesis. This application shows that the optimized fQSM combined with MEG has potential for application to long-term and interventional clinical research to observe the blood oxygen and neural activity, which is believed to be of great benefit to precision medicine in neuroscience. More studies in MRS is required to have more significant results.

Title of Project: Cold Atmospheric Plasma-reinforced Micro/Nano-Biomimicked Hybrid Carrier Loaded with Platelet Lysate for Enhanced Osteoarthritis Attenuation

Project No.: NHRI-EX114-11323EI

P.I.: Er-Yuan Chuang/莊爾元

Key Professional Personnel: Er-Yuan Chuang/莊爾元, Chih-Hwa Chen/陳志華, Burnouf, Thierry P. R./白台瑞

Affiliation/Institution: Taipei Medical University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Osteoarthritis (OA) is commonly managed with nonsteroidal anti-inflammatory drugs (NSAIDs) or hyaluronic acid injections, which primarily provide symptomatic relief without preventing the progression of cartilage degradation. Platelet lysate (PL), rich in growth and trophic factors, has emerged as a potential regenerative therapy for cartilage repair. Nevertheless, its direct intraarticular application is hindered by limitations such as rapid dispersion, protein instability, short bioactive lifespan, and risks associated with repeated injections. Many existing approaches overlook the inherent biological properties of PL and simply blend it into scaffold materials. In contrast, this study introduces a novel micro/nano-scale PL delivery system stabilized by cold atmospheric plasma (CAP)-induced crosslinking of F127, glycol chitosan, and hyaluronic acid. This engineered formulation enhances material performance, enables sustained release, and may provide targeted delivery to diseased tissues. The proposed strategy is anticipated to maximize the therapeutic benefits of PL in OA management. Notably, this is the first report to incorporate the intrinsic properties of PL into the rational design of a CAP-enhanced biomaterial, with comprehensive evaluation of its biological function and mechanistic impact in both *in vitro* and *in vivo* models.

Title of Project: Using Artificial Intelligence to Assist with Transcatheter Aortic Valve Implantation Procedure Planning and Predict Patient Outcomes

Project No.: NHRI-EX114-11324EI

P.I.: Yu-Te Wu/吳育德

Key Professional Personnel: Wei-Hsian Yin/殷偉賢, Yung-Tsai Lee/李永在, Yun-Hsuan Tzeng/曾芸軒, Ho-Ren Liu/劉浩仁, Chi-Wen Jao/饒啟文, Jia-Sheng Hong/洪佳聖, Guan-Yu Li/李冠昱, Kuan-Ting Wu/吳冠廷, Huan-Yu Hsu/許桓瑜, Shih-Yu Huang/黃詩諭

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

This project's Aim1(1st year) is to develop and validate a deep learning model that automates the detection and quantification of aortic valve hinge points across the cardiac cycle in cCTA images, precisely localizing the annulus plane. The Aim2(2nd year) focuses on segmenting and labeling aortic and aortic valve calcifications to calculate calcium scores. Subsequently, we'll investigate the relationship between cardiovascular calcification and multiphase quantitative changes in the aortic root, enhancing our understanding of vascular calcification characteristics. **Introduction:** Aortic stenosis (AS) is a prevalent and potentially fatal valvular heart disease common in the elderly. Its severity progresses with age, characterized by a narrowing of the aortic valve opening. While surgical aortic valve replacement (SAVR) and TAVI are primary treatments, accurate preoperative anatomical assessment via cCTA is crucial for TAVI given its minimally invasive nature. Currently, no fully automated tool comprehensively quantifies calcification in the thoracic aorta, aortic-valve annulus, and coronary arteries—all vital for TAVI sizing and risk assessment. Clinicians typically rely on single-phase imaging, overlooking the dynamic deformation of the aortic root throughout the cardiac cycle and how calcific stiffness alters this motion. **Methodology:** This study retrospectively collected data from 185 TAVI cases at Cheng-Hsin General Hospital from 2013 to 2022. These patients were considered high-risk and unsuitable for SAVR due to severe aortic stenosis. The collected data included cCTA images obtained during preoperative TAVI assessmentsOur two-step approach first uses a model to isolate a 3D region of interest (ROI) containing spherical segmentation masks centered on the three aortic valve hinge points and two coronary artery ostia. A second model then predicts the 3D ball masks for these five points within the isolated ROI. We calculate the centroids of these predicted spheres and map them back to the original image to obtain the model-predicted coordinates for the hinge points. The aortic valve annulus area is subsequently segmented on 2D CT images, defined by the coplanar relationship of these three hinge points. To automatically detect valvular calcification (AVC) in cCTA images, we developed an nn-Unet-based model to calculate calcium scores. Finally, we compared the changes in annulus area with the severity of calcification to understand their interrelationship. **Results:** We evaluated our coordinate point detection models using Euclidean distance error for point precision, angular error for coplanar surface alignment, and absolute height error for coronary artery ostia. Our CNN-powered annulus segmentation model successfully automated cardiac cycle area curve plotting, achieving a Dice Similarity Coefficient (DSC) of 0.98. For AVC segmentation, our model achieved a DSC of 0.793±0.102 (median: 0.824). Analysis of 142 contrast-enhanced CT studies showed that increasing cusp calcification correlates with a larger annulus. From the lowest (Q1) to highest (Q4) quartiles of AVC volume, the mean annular area increased by 29% (from 401 mm^2 to 516 mm^2), and mean maximal diameter increased by 2.3 mm (from 20.6 mm to 22.9 mm). The broadest interquartile range in Q4 suggests greater geometric variability with dense calcium. These results confirm that more severe aortic valve calcification systematically corresponds to a larger aortic root, a critical factor for device sizing and sealing. We observed strong linear correlations between calcium load and annular area (r=0.55), maximal diameter (r=0.53), and minor diameter (r=0.42). Quantitatively, every 1000 mm^3 increase in AVC volume was associated with an approximate 11 mm^2 increase in surface area or 0.3 mm increase in width.

Title of Project: Preclinical Study of Innovative High-entropy Alloy Stent Graft for Abdominal Aortic Aneurysm Repair

Project No.: NHRI-EX114-11325EI

P.I.: Ming-Long Yeh/葉明龍

Key Professional Personnel: Ming-Long Yeh/葉明龍, Jun-Neng Roan/阮俊能, Chuan-Feng Shih/施權峰

Affiliation/Institution: National Cheng Kung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

The stent graft serves as an intravascular device designed to repair abdominal aortic aneurysms by replacing the compromised vascular wall and restoring normal blood flow, thereby reducing the risk of rupture. However, the occurrence of endoleak, which arises from the displacement of the implant due to inadequate mechanical properties, remains a significant challenge in clinical practice. To address these complications, it is crucial to improve the radial compliance and longitudinal flexibility of stent grafts. High-entropy alloys, recognized for their exceptional mechanical properties resulting from diverse elemental compositions and crystal structures, present a promising approach for enhancing stent grafts.

This study focused on the fabrication of CuCoZrNbAl high-entropy alloy with varying aluminum concentrations. The alloy was produced by molding metal powder using a hydraulic press, followed by die casting under a pressure of 50 kN. The resultant metal ingot was subjected to heat treatment for varying durations of 30 s, 60 s, and 90 s, accompanied by quenching cycles of 1, 3, and 5 times, to evaluate their effects on the material's properties. A series of experimental methodologies, including surface analysis, mechanical property assessments, and biocompatibility evaluations, was employed to investigate the alloy's suitability as a material for stent graft applications.

Surface analysis revealed that the duration of the heat treatment significantly influences surface properties, with a period of 60 s deemed optimal for heat treatment. This specific duration promotes uniform melting by mitigating the presence of distinct grain boundaries. Additionally, among the various experimental compositions, $CuCoZrNbAl_{0.7}$ exhibited improved surface uniformity. In the elastic reciprocating performance assessment, $CuCoZrNbAl_{0.7}$ also showed superior elastic characteristics, surpassing those of $CuCoZrNbAl_{1.0}$. This enhancement could be attributed to the incomplete precipitation of aluminum within this group, which prevents the development of substantial cracks that could compromise the material's mechanical properties.

Furthermore, $CuCoZrNbAl_{0.7}$ demonstrated favorable cellular compatibility. This observation indicated that the proliferation and migration of vascular endothelial cell colonies may facilitate enhanced intercellular interactions, which could lead to improved endothelialization of blood vessels and expedited tissue repair processes. In summary, the results of this study can serve as a foundational reference for advancing a stent graft, thereby expanding the range of interventional treatment options available.

Title of Project: Application of Multi-contrast Optical Coherence Tomography in Early Oral Cancer and Tumor Margin Detection

Project No.: NHRI-EX114-11326EI
P.I.: Wen-Chuan Kuo/郭文娟
Key Professional Personnel: Hiu-Ki Lai/賴曉琪, Chung-Yu Chang/張重育
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Oral cancer has been one of the top ten cancers in Taiwan since 1991 and remains so today. Inspection of Oral Mucosa relies on the doctor's visual or palpation to determine whether there are abnormal lesions and to perform a biopsy to obtain analysis results. There is a lack of tools that can quickly distinguish between benign and malignant tumors. Optical coherence tomography (OCT) has the advantages of rapid scanning, large-range scanning, quantitative analysis, and no need for contrast agents. It has the potential to be used as a new tool for early diagnosis of oral cancer. Using polarization-sensitive optical coherence tomography (PS-OCT) could provide additional tissue information that may help in cancer diagnosis.

During the first and second year of study, we aim to validate multi-contrast PS-OCT with the addition of derived parameters for improved diagnosis, early detection and even prediction of oral cancer in an animal model. A longitudinal study was conducted, with various stages of change being recorded and analyzed to evaluate the relationship between cancer development and stromal change. To induce tumorigenesis, 100 mg/mL of the water-soluble carcinogen 4NQO (Sigma-Aldrich, St. Louis, MO, United States) was added to the drinking water of six-week-old, K14-EGFP-miR-211-GFP transgenic mice for 12 weeks. The experiments were performed in weeks 20, 24, and 26 after the commencement of cancer induction. The steps of the experiment were as follows: (1) the mouse was anesthetized by intraperitoneal injection of 2,2,2 tribromoethanol (200 mg/kg); (2) the anterior part of the tongue was gently extended, fixed, and scanned by multi-contrast OCT *in vivo*; (3) after image acquisition, the mouse was sacrificed, the whole tongue was extracted, after which the histological slides were stained with H&E and Masson’s trichrome staining.

We incorporate several PS-OCT derived parameters, such as differential intensity, differential phase retardation, degree of polarization uniformity (DOPU), and fast axis. This study has conducted a long-term follow-up observation experiment on oral cancer mice (Normal N=3, Hyperplasia N=3, CIS N=2), and provided objective functional images for comparison with histological pathological sections and used the changes in phase delay signals to locate tumor-related areas accurately. We observed the changes in relative values of parameters of tumors at the same location in mice during different cycles, among which the changes in carcinoma in situ (CIS) were significantly different from the development trend of normal mice. The study verified that multi-contrast PS-OCT is effective in helping to determine benign and malignant lesions.

Title of Project: High-resolution Ai Assisted Varifocal Endomicroscopy for *in-vivo* Brain Imaging Using Metalens

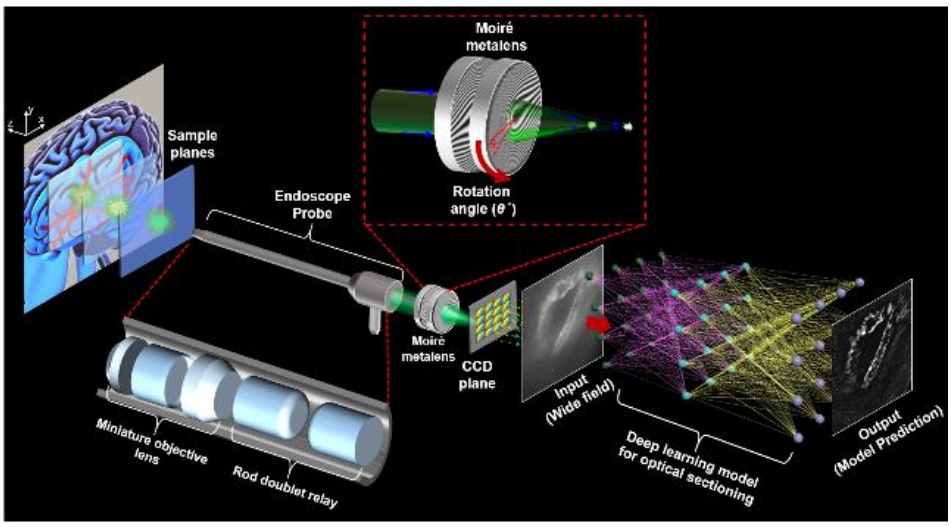
Project No.: NHRI-EX114-11327EI

P.I.: Yuan Luo/駱遠

Key Professional Personnel:

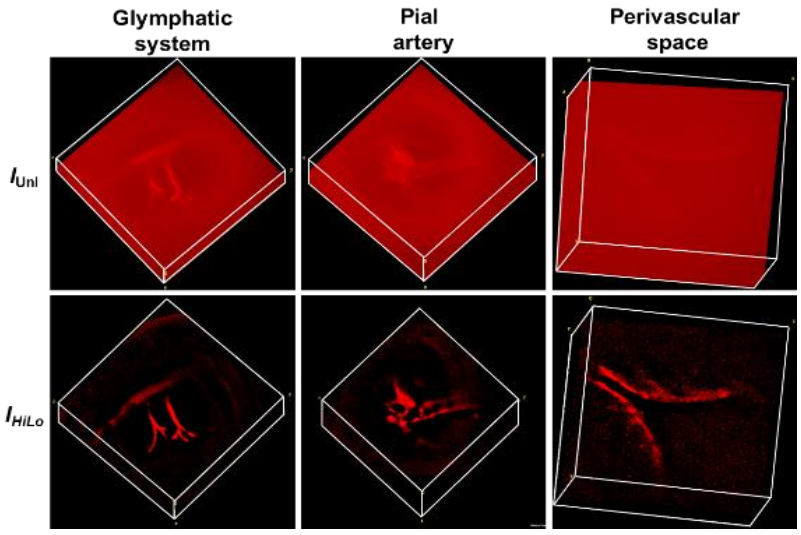
Affiliation/Institution: National Taiwan University

Entire Project Period: From 2024 to 2026 (Total: 3 years)



High-resolution AI assisted varifocal endomicroscopy for in-vivo brain imaging using metalens

Endo-microscopy with structured illumination HiLo imaging process can provide sectioning ability. However, moving optical elements in the axial direction for the 3D imaging restricts compact endoscopic system design. In addition, HiLo imaging requires multiple shots, which is time-consuming and make system configuration complicated. Here, we propose a high-resolution AI assisted varifocal endomicroscopy for mouse brain imaging using metalens. With the telecentric design, the endo-microscopy can provide constant magnification during axial scanning for mouse brain 3D imaging of mouse brains. Furthermore, we introduce the deep learning (DL) network for HiLo sectioning technique, which can substantially reduce image acquisition time and system complexity.



The 3D *ex-vivo* mouse brain images (750μm×750μm×1mm).

Title of Project: Objective Measurement-based Cochlear Implant Programming
Project No.: NHRI-EX114-11328EI
P.I.: Charles Tak Ming Choi/蔡德明
Key Professional Personnel:
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Typically, 3–6 weeks after cochlear-implant (CI) surgery, every recipient undergoes an initial fitting (or mapping). During this session, the audiologist must establish the most comfortable level (MCL) for each of the 16 electrodes. The conventional method relies primarily on behavioral feedback, where the patient indicates whether each stimulus is audible and comfortable. Even in adults, this is time-consuming; in infants and toddlers—who account for 40–50 % of new CI recipients annually and lack the communication skills to respond reliably—it is exceptionally challenging.

Behavioral fitting remains the gold standard, yet it is labor-intensive. For pediatric users, it takes approximately two hours to obtain MCLs for only four electrodes (sampled from the apical, mid-apical, mid-basal, and basal regions). In older children or adults, the same task requires 60–90 minutes. The four measured MCLs are then interpolated to estimate values for the remaining 12 electrodes, resulting in an average MCL error of 7–8% and could be as high as 35%.

Compounding this burden, MCLs drift during the first postoperative year and must be readjusted five to six times before stabilizing 8–12 months after surgery.

Accordingly, there is an unmet clinical need for: A non-behavioral fitting approach that lowers stress for CI users aged 1–6 years, and an autonomous system that reduces clinic time for all CI users.

Proposed solution – Patient-specific cochlear-implant model (個人化人工耳蝸模型)

Our approach combines limited behavioral data with objective measurements: Measure behavioral MCLs at four evenly spaced electrodes. Acquire objective measurements from the remaining 12 electrodes. Use a patient-specific computational model to predict MCLs for those 12 electrodes.

Preliminary results reduce the average MCL prediction error from 7–8 % to < 1 %, a magnitude likely to benefit early speech and language development in pediatric CI users.

Today, all three major CI manufacturers restrict remote fitting to patients aged 12 years or older (and only after initial activation). By enabling accurate, model-based predictions, the proposed technology could extend remote fitting to younger children, thereby sparing families the need for repeated clinic visits and further streamlining adult care.

Title of Project: Self-packaging Pseudovirus-like Nanoparticle for *in vivo* RNA Delivery and Cancer Immunotherapy

Project No.: NHRI-EX114-11329EI

P.I.: Yu-Chen Hu/胡育誠

Key Professional Personnel: Dang Thuc Quyen/鄧杜娟, Truong Anh Vy/張英偉, Pin-Yan Chen/陳品諺

Affiliation/Institution: National Tsing Hua University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Self-packaging Pseudovirus-like Nanoparticle for RNA Delivery

Protein-based nanoparticles (PBNPs) are a novel mRNA delivery system. When the human endogenous PEG10 protein recognizes the untranslated region (UTR) of its own mRNA, it enables self-assembly into nanoparticles within the cell. Compared to lipid nanoparticles (LNPs), PBNPs have a structure derived from humanized genes, which can reduce immune rejection and cellular defense mechanisms. Additionally, the production process of PBNPs is more convenient. Therefore, PBNPs represent a highly promising non-viral vector for gene therapy.

Here, we developed a human PBNPs platform for cargo RNA self-packaging and delivery for cancer therapy. We designed a baculovirus (BV) system to replace the conventional plasmid transfection system. Compared to plasmid transfection, BV yielded 11.3-fold more PBNPs at reduced cost, leveraging its high transduction efficiency in mammalian cells and compatibility with large-scale vaccine production infrastructure. The PBNPs were capable of self-packaging long mRNA transcripts (>7 kb) flanked by PEG10 UTRs and remained stable at 4°C for up to seven months. To enhance cancer cell specificity, engineered PBNPs (ePBNPs) displaying EGFR-targeting scFv-VSVG demonstrated significantly improved delivery efficiencies, up to 71% in colon cancer cells. The modularity of ePBNPs also enabled delivery of immunostimulatory mRNAs (e.g., IL-12/OX40L), induced significantly higher IL-12/OX40L expression, cytokine secretion (IFN-γ, TNF-α), splenocyte proliferation, and CD4+/CD8+ T cell activation compared to controls. These results demonstrate that ePBNP.OI effectively stimulates T cell responses through paracrine signaling.

Overall, this study establishes a robust production platform and highlights the potential of PBNPs as a novel and effective RNA delivery system.

Title of Project: Application of PBX1 Inhibitors Derived from Mesoporous Silica Nanoparticles to Overcome the Cancer Stem Cell Properties Induced by Gemcitabine in Chemoresistant Pancreatic Cancer Cells

Project No.: NHRI-EX114-11404EI
P.I.: Yao-An Shen/沈耀安
NHRI Researcher: Leu-Wei Lo/羅履維
Key Professional Personnel: Yu Hsin Lin/林妤芯, Zhu-Chen Hung/洪子宸
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a five-year survival rate below 5%, primarily due to chemoresistance and early metastasis. Gemcitabine, the frontline chemotherapeutic agent, fails to eliminate cancer stem cells (CSCs)—a tumor-initiating subpopulation characterized by self-renewal, plasticity, and resistance to cytotoxic stress—thereby contributing to disease recurrence. We identified PBX1, a transcription factor involved in chromatin remodeling and oncogenic signaling, as a key driver of CSC enrichment in gemcitabine-resistant PDAC. Gemcitabine exposure in PANC-1 and MIA PaCa-2 cells induced a ~165-fold increase in PBX1 expression, accompanied by upregulation of EMT transcription factors (TWIST, ZEB1, SNAIL, SLUG), stemness markers (OCT4, SOX2), and multidrug resistance transporters (ABCB1, ABCA3, ABCA7). Functionally, resistant cells exhibited increased migration, invasion, and spheroid-forming capacity, consistent with a CSC-like phenotype. To therapeutically target PBX1, we developed pH-responsive mesoporous silica nanoparticles (MSN–PBX1i) encapsulating two small-molecule inhibitors (B004, T417). Both formulations demonstrated efficient loading and pH-triggered release, with MSN–B004 showing faster but less selective release, while MSN–T417 provided tighter tumor-specific release kinetics. In 3D spheroid models, MSN–B004 exhibited the lowest IC_{50} and strongest anti-CSC activity, whereas MSN–T417 offered improved tumor selectivity with reduced off-target cytotoxicity. Together, these findings highlight PBX1 as a central mediator of chemoresistance and CSC plasticity in PDAC and support MSN–PBX1i as a promising therapeutic strategy for overcoming gemcitabine-induced resistance.

Title of Project: Development of Advanced Personalized EEG-Guided Brain Stimulation for Depression

Project No.: NHRI-EX114-11418EC
P.I.: Chun-Shu Wei/魏群樹
Key Professional Personnel: Pin-Hsuan Chao/趙品瑄, Yu-Cheng Chang/張祐誠, Chern-Tay Shih, Li-Fen Chen/陳麗芬, Wei-Chung Mao/毛衛中, Tung-Ping Su/蘇東平
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Repetitive transcranial magnetic stimulation has entered the clinic, yet objective evidence for real-time phase-locked protocols remains limited. We present a validation framework that rigorously quantifies the temporal precision of a prototype theta-burst stimulation (TBS) platform designed to lock bursts to endogenous electroencephalographic rhythms.

The system integrates a 32-channel EEG front-end, a MATLAB-based online engine, and a commercial stimulator. To assess its performance we devised a two-tier strategy. First, in-silico replay of seventy-six minutes of resting EEG from nineteen healthy adults generated 7,600 virtual triggers across four target phases. Second, the same EEG was converted to an analogue signal, injected into a saline phantom, and re-recorded while the stimulator delivered genuine magnetic pulses, yielding a further 180 triggers.

Across algorithms, best-case offline replay achieved a mean absolute phase error of 0.86 rad with a 74 % success rate and no evidence of dead-locking; inter-burst intervals clustered tightly between 9.8 and 12.6 s. Phantom experiments reproduced these figures within statistical error (mean absolute timing error 0.12 s, success rate 0.67). A strong correlation ($r = 0.89$) emerged between algorithmic circular error and real-world trigger error, validating the predictive value of the offline metric suite.

These results show that sub-millisecond phase alignment is feasible in TBS without compromising burst-train spacing, and they establish an open benchmark for cross-laboratory comparison. By separating evaluation tooling from adaptive control logic, the framework enables transparent reporting today while safeguarding forthcoming innovations in personalised stimulation.

Title of Project: Improving Care Coordination for Patients with Polypharmacy: the Development and Evaluation of a De-prescribing Program
Project No.: NHRI-EX114-11001PI
P.I.: Shou-Hsia Cheng/鄭守夏
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2021 to 2025 (Total: 5 years)

Evaluating the Effects of the National Health Insurance Inpatient Medication Quality Improvement Program.

Background: In response to the rising prevalence of chronic diseases, the National Health Insurance (NHI) Administration collaborated with the Taiwan Pharmacists Association to launch the Inpatient Medication Quality Improvement Program in 2019. This initiative provides medication review services during hospitalization, aiming to enhance the quality of medication use among patients.

Objective: To evaluate the effectiveness of the NHI Inpatient Medication Quality Improvement Program.

Methods: This study utilized a natural experimental design with data extracted from the nationwide NHI claims data between 2019 and 2024. The study population consisted of elderly patients with stable hypertension who had been admitted to intensive care units (ICUs). The intervention group comprised 12,309 patients enrolled in the Inpatient Medication Quality Improvement Program during this period, while an equal-sized comparison group was selected by propensity score matching approach. The outcome measures included (1) the proportion and number of days with duplicate medications prescribed across different visits by different physicians, and (2) the proportion and number of potentially inappropriate medications (PIMs), as defined by the Beers Criteria. Medication use was assessed for the 30 days prior to ICUs admission and the 30 days following ICU discharge. Generalized estimating equations (GEEs) models using a differences-in-differences approach were employed to examine the effects of this program.

Results: During the observation period, a total of 63,922 elderly patients with stable hypertension were admitted to hospital ICUs. Among them, 12,309 patients received the Inpatient Medication Quality Improvement Program. After propensity score matching, both the intervention and control groups consisted of 12,147 patients. Preliminary results indicated a reduction in duplicate medication use after discharge: the rate declined from 16.39% to 14.74% in the intervention group, while in the comparison group, it increased from 17.28% to 18.32%. The prevalence of PIMs declined in both groups: from 62.39% to 42.89% in the intervention group, and from 62.61% to 51.80% in the comparison group. Results from the GEEs models showed that the intervention group had a 19% lower likelihood of post-discharge duplicate medication use compared to the comparison group (odds ratio [OR] = 0.81, 95% confidence interval [CI]: 0.74–0.90). In addition, the number of days with duplicate medications was lower in the intervention group ($\beta = -0.13$, $P = 0.05$). Regarding PIMs use, the intervention group had a 32% lower likelihood of PIMs (OR = 0.68, 95% CI: 0.63–0.74), and the average number of PIMs per day was also slightly reduced ($\beta = -0.04$, $P < 0.01$).

Conclusion: This study demonstrates that the NHI Inpatient Medication Quality Improvement Program has achieved its preliminary objective of reducing medication duplication and PIMs in patients with hypertension admitted to ICUs. However, the persistently high rates of both medication duplication and PIMs highlight the need for continued monitoring and further investigation into underlying causes and the development of potential system-level interventions.

Title of Project: A Novel Multi-dimensional Prospective Study of the Gut-brain Axis Through Metabolic MRI, Metabolomics and Gut Microbiome to Discover Gene-microenvironment Interactions in Neurodevelopmental Disorders

Project No.: NHRI-EX114-11002PI
P.I.: Susan Shur-Fen Gau/高淑芬
Key Professional Personnel: Yen-Hsuan Ni/倪衍玄, Wen-Chau Wu/吳文超, Yufeng Jane Tseng/曾宇鳳, Hsin-Chou Yang/楊欣洲, Chi Yung Shang/商志雍, Yi-Ling Chien/簡意玲
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2021 to 2025 (Total: 5 years)

Background: Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are prevalent neurodevelopmental conditions with lasting impacts. Despite distinct diagnostic criteria and interventions, they may share genetic and neurobiological susceptibilities. This five-year project integrates gut-brain axis and whole-body metabolic research to identify shared and disorder-specific biomarkers and explore gene-microenvironment interactions. **Methods:** We collected clinical symptoms/diagnoses, psychosocial functions, neuropsychology, neuroimages [T1, T2, diffusion tensor image (DTI), resting-state fMRI, MRS), metabolites (blood), and intestinal microbiome (stool) from 170 children with ASD, 143 children with ADHD, and 166 typically developing controls (TDC) aged 4-12 years at Time 1. At Time 2 (follow-up after 2-4 years), 213 subjects completed the same repeated measures (105 ASD, 46 ADHD, 62 TDC). We integrated the multi-dimensional data and conducted experimental, image, multi-omic, and correlation analyses. **Results:** ASD showed the most severe autistic symptoms, followed by ADHD, and TDC the least. Both clinical groups exhibited elevated symptoms of inattention, hyperactivity-impulsivity, and oppositionality. Preliminary microbiome analyses revealed no significant differences in F/B ratio, relative abundance, or alpha diversity; however, they did show differences in beta diversity. LDA revealed higher Coriobacteriia and Lachnospiraceae in ASD, Bacteroidetes and Cutibacterium in ADHD, and higher Oscillospiraceae and Dialister in TDC. Across gray matter volume, cortical thickness, and surface area, bilateral cortical regions showed group differences, including the anterior cingulate, superior parietal lobule, postcentral gyrus, precuneus, superior temporal gyrus, occipital pole, and insula. These regions encompass sensory processing (postcentral gyrus, occipital pole), cognitive control and attention (anterior cingulate, superior parietal lobule), and social-emotional domains (precuneus, superior temporal gyrus, insula), with bilateral alterations suggesting system-level disruptions in interhemispheric coordination. DTI revealed widespread white matter microstructural alterations in ASD, including elevated fractional anisotropy (FA) in the corpus callosum and cerebellum, and broadly increased mean diffusivity (MD) with corresponding changes in axial diffusivity (AD) and radial diffusivity (RD). ADHD children showed fewer, more localized changes—some increases in FA or AD in cerebellar regions, but more commonly lower MD in association fibers and widespread reduced AD. MD values in the right corticospinal tract and cerebellum were positively correlated with Lachnospiraceae and negatively with Cutibacterium. **Discussions:** This five-year project is in its final phase of multi-dimensional data collection. Due to the high cost of microbiome and metabolomic analyses, we plan to seek additional funding to complete comprehensive three-group, two-wave analyses next year. Preliminary findings reveal distinct microbiome profiles in ASD and ADHD. Morphometric results indicate widespread cortical disruptions affecting sensorimotor, executive, and socio-emotional functions, which are linked to key networks such as the salience, default mode, and social cognition networks. ASD exhibits atypical white matter development, characterized by both early over-coherence and delayed maturation across significant tracts. ADHD is characterized by reduced axonal integrity in association and projection fibers, with increased FA or AD in cerebellar regions, possibly reflecting delayed pruning. Longitudinal analyses will further explore gut-brain axis differences in both disorders.

Title of Project: Novel Brain Neurotechnology for Optimizing Precision Mirror Therapy in Stroke
Project No.: NHRI-EX114-11105PI
P.I.: Ching-Yi Wu/吳菁宜
Key Professional Personnel: Ching-Yi Wu/吳菁宜, Chia-Ling Chen/陳嘉玲, Ku-Chou Chang/張谷州, Yu-Wei Hsieh/謝妤葳, Chien-Ting Liu/劉建廷, Pei-Kwei Tsay/蔡培癸
Affiliation/Institution: Chang Gung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Stroke often results in persistent motor impairments and difficulties with daily functioning. Motor rehabilitation is important for motor recovery and functional independence. Although various neural markers and therapeutic models have been proposed, treatment effects beyond primary motor function—such as ADL—often remain inconsistent. The combination of mirror therapy and transcranial direct current stimulation (tDCS) has recently shown promise. Building on this, we conducted a series of clinical studies to optimize this combined protocol. These were based on the gating-by-inhibition model, which suggests that cortical alpha power regulates activity by gating neural resources for motor recovery. Previous research links temporal lobe activity with verbal interference, which may hinder rehabilitation. We therefore hypothesized that higher alpha power in the temporal lobes would contribute to motor recovery. To test this, we examined the relationship between electroencephalogram (EEG) alpha power and clinical outcomes in stroke patients who underwent mirror therapy following tDCS (targeting either the premotor cortex [PMC], primary motor cortex [M1], or sham). As predicted, reduced alpha power was significantly associated with Fugl-Meyer Assessment (FMA) improvements 3 months later, but only in the PMC-tDCS group. Additionally, baseline alpha power in temporal and central regions predicted later FMA scores. This research highlights temporal alpha power as a potential predictive marker for rehabilitation outcomes.

Our second study further examined the correlations between alpha power in two cortical regions and various clinical measures, particularly those related to ADL, across different levels of ADL complexity. The correlation results revealed two distinct patterns. As in the previous study, temporal alpha power was consistently associated with a range of ADL measures, but only in the PMC-tDCS group. In contrast, another correlation pattern was found in M1-tDCS group with central-frontal alpha power was positively associated with improvements in simple ADL but negatively associated with recovery in complex ADL tasks. This suggests alpha power in the central-frontal region (M1) depended on the complexity of the ADL function. These two distinct correlation patterns observed in the PMC-tDCS and M1-tDCS groups suggest the existence of two potential therapeutic mechanisms for supporting ADL function. Overall, this series of studies demonstrates the utility of EEG alpha power as a predictive index for FMA recovery and its relevance to ADL performance. Importantly, our findings show for the first time that reduced alpha power in non-motor regions—specifically the temporal lobes—can be beneficial for neurorehabilitation in stroke patients. This suggests that directing neural resources from non-motor regions may be a critical mechanism underlying effective neurostimulation treatments for stroke recovery.

Title of Project: Digital Dyadic Empowerment Program on Lifestyle Modification for Chronic Kidney Disease Management

Project No.: NHRI-EX114-11106PI
P.I.: Miao fen Yen/顏妙芬
Key Professional Personnel: Chun-Yi Ho/何俊毅
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Background: The long-term management of chronic kidney disease (CKD) requires active participation from patient-caregiver dyads in lifestyle modification. Our LINE-based digital platform "*Kidney Lifestyle*" aims to empower CKD dyads in modifying their lifestyles.

Objective: To assess the feasibility of a full-scale randomized controlled trial (RCT) comparing Digital Dyadic Empowerment Program (DDEP) to usual care for CKD management.

Methods: This was a three-month, two-arm, parallel-group randomized controlled feasibility trial conducted in the nephrology outpatient clinics of a medical center in Tainan, Taiwan, from January to November 2024. Eligible CKD patient-caregiver dyads (age ≥ 20 years) using LINE app regularly were randomized in a 1:1 ratio to receive either the DDEP + usual care (intervention group) or usual care only (control group). The intervention group used our digital platform to monitor their daily physiological data, diet, medication adherence, and exercise at home. Feasibility criteria included: (1) monthly recruitment of ≥ 30 CKD dyads, (2) study completion rate ≥ 80% in both groups, (3) intervention acceptability indicated by a 90-day platform usage rate (daily usage record) ≥ 50% among intervention participants, and (4) adverse event rate < 5%.

Results: Within 46 days, 60 eligible dyads were recruited from 2,214 screened CKD patients, meeting the expected feasibility criterion for recruitment. The study completion rate was 91.67% (55/60, 95% CI [81.93, 96.39]), with 4 dyads from the intervention group and 1 dyad from the control group dropping out. Attrition was primarily due to older age and caregiver workload. There were no significant differences in attrition, baseline demographic or clinical characteristics between the two groups (*p*s > .05). For intervention acceptability, the 90-day platform usage rate for the 26 dyads who completed the study was 48.93% (1,145/2,340[26×90], 95% CI [46.91, 50.96]), slightly below the 50% target. Platform usage showed a clear bimodal distribution: 14 high-usage dyads (average 87.06%, 1,097/1,260[14×90], 95% CI [85.10, 88.80]) reported benefits including improved biochemical parameters, effective caregiver support, and enhanced adherence to self-monitoring; whereas the other 12 low-usage dyads (average 4.44%, 48/1,080[12×90], 95% CI [3.37, 5.84]) generally found daily logging burdensome. There were no significant differences in baseline demographic or clinical characteristics between the high- and low-usage groups (*p*s > .05). However, high usage was slightly associated with later recruitment timing ($\chi^2[1] = 3.87$, $p = .049$). One dyad from the intervention group withdrew due to psychological burden, which was not classified as an adverse event. Thus, the adverse event rate was 0% (0/60, 95% CI [0, 6.02]).

Conclusions: This study demonstrates the feasibility of a full-scale RCT for the DDEP, with promising recruitment scalability, high study completion rates, and positive feedback from participants. However, with an overall average platform usage rate of less than 50%, intervention acceptability needs improvement. A formal RCT will extend the follow-up period to six months to evaluate the long-term effects of the program, while addressing tracking bias and reducing the risk associated with low platform usage rates.

Trial registration: ClinicalTrials.gov identifier NCT06226649

Title of Project: The Effect of Early Life Exposure to Emergent Environmental Pollutants on Child Development: a Cohort Study Based on Taiwan Southern Human Milk Bank

Project No.: NHRI-EX114-11116PI
P.I.: Yung-Chieh Lin/林永傑
NHRI Researcher: Po-Chin Huang/黃柏菁
Key Professional Personnel: Pao-Lin Kuo/郭保麟, Yu Tsung/余聰, Wei-Hsiang Chang/張偉翔
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Background/Study Aims: Phthalates and their substitutes, including new emergent environmental plasticizers (NEEP), are endocrine-disrupting chemicals (EDCs) linked to adverse health outcomes, particularly in pregnant women, fetuses, and infants. The specific risks posed by NEEP to these vulnerable groups remain largely uncharacterized, and human milk represents a plausible, under-investigated route for maternal NEEP exposure to infants. This longitudinal study aimed to quantify maternal and infant exposure to NEEP through blood, urine, and human milk samples collected from pregnancy through early childhood, and to evaluate potential long-term impacts on infant health, hormonal systems, and neurodevelopment.

Methods: This 4-year prospective cohort study (2022–2025) recruited **600** pregnant participants. Maternal blood, infant urine, maternal urine, and human milk samples were collected. Maternal blood was analyzed for thyroid function tests (TFT). NEEP concentrations were quantified in urine and human milk samples at the National Health Research Institutes (NHRI). Demographic information, medical histories, physical examinations, and anthropometric measurements were collected.

Results: Over 3.5 years, **557** maternal participants were enrolled, with **383** infants included. Biological samples analyzed included urine from 281 mothers and 341 infants, serial human milk from 314 mothers, and TFT from 363 mothers and 382 infants. **Perinatal urine** phthalate metabolite concentrations were analyzed (mean[median] ng/ml): MMP 20.9[15.0], MEP 83.7[18.1], MiBP 11.8[5.9], MnBP 20.4[8.4], MBzP 2.5[0.0], MEHP 13.2[5.4], MEHHP 17.9[8.7], MEOHP 19.3[11.5], MECPP 17.0 [9.4], MCMHP 7.5 [4.3], and MiNP 2.8 [0.0] **for mothers**; MMP 29.1 [7.2], MEP 125.4[34.2], MiBP 14.0[7.9], MnBP 15.2[8.3], MBzP 18.2[2.5], MEHP 54.5[13.8], MEHHP 18.5[2.9], MEOHP 27.6[3.3], MECPP 84.4 [7.9], MCMHP 14.3 [0.0], and MiNP 1.6 [0.0] **for infants**. Phthalate metabolites were studied in **human milk** from 244 mothers. Most plasticizers were detected in >90% of samples. Significant variability was observed for several plasticizers, with some samples showing exceptionally high concentrations. MiDP and MEHHP were rarely detected, while MEHP and MiNP were detected less frequently but at relatively high concentrations. In infants and mothers, none of the urine phthalate metabolites showed a statistically significant correlation with TSH at birth (all p-values > 0.05). However, in the **maternal** perinatal urine and serum free T4: higher concentrations of MECPP and MCMHP were associated with lower FreeT4 levels in this study population. The associations for MEHHP and MiNP were close to significance but did not reach the conventional threshold.

Conclusion: This cohort study demonstrates comparable levels of urine phthalate metabolites between infants and mothers, with infant MEHP levels occasionally higher, suggesting potential transplacental and lactational transfer. These findings underscore the need for continued vigilance regarding phthalate exposure during pregnancy and lactation, and highlight the importance of long-term follow-up to assess potential health impacts on exposed infants.

Title of Project: Interactions Between Host Immunogenetic Variants and Epstein-Barr Virus Antibody Responses on the Risk for Nasopharyngeal Carcinoma: A Large-Scale Case-Control Study
Project No.: NHRI-EX114-11117PI
P.I.: Mei-Hsuan Lee/李美璇
Key Professional Personnel: Szu-Ching Yin/尹思晴; Wan-Lun Hsu/徐婉倫; Chien-Jen Chen/陳建仁; Cheng-Ping Wang/王成平
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Nasopharyngeal carcinoma (NPC) is a rare cancer that exhibits familial clustering. In Taiwan, the incidence of NPC is relatively high compared to other countries. Epstein-Barr virus (EBV), which infects more than 90% of adults worldwide, is a well-known determinant contributing to the development of NPC. However, the extent to which genetic alterations influence EBV control and its association with NPC remains incompletely understood. The human leukocyte antigen (HLA) region, known for its complex nature within the human genome, plays a crucial role in immune responses to clear foreign antigens. Despite extensive research on EBV and HLA, the interactions between host genetic variants and virus controls in relation to NPC have received limited attention. Therefore, we proposed a large-scale case-control study involving 1,998 NPC cases and 2,131 unaffected controls. The aim of this study is to investigate the associations of *HLA* variants and the interplay between specific *HLA* alleles and EBV antibody-based signatures in determining the risk of developing NPC. From Jan 2022 to May 2025 we have performed 3170 samples for whole-genome SNP array (TWB 2.0) which includes 686,389 variants in the human genome. Among the 3170 samples, 3088 (1402 NPC cases and 1686 controls) were successfully genotype and passed the quality control. All of these samples were performed for subsequent analyses. There were 74% (2276/3088) males; the mean age was 48.1 years old. The blood samples were collected and tested for IgA antibodies against EBV viral capsid antigen (VCA) and nuclear antigen 1 (EBNA-1). Amongst total samples, 23% and 32% were seropositive for EBNA-1 and VCA IgA, respectively. More NPC cases were seropositive for either EBNA-1 and VCA IgA, by comparing to unaffected controls ($p<0.001$). We may impute the 8 major HLA genotypes, including class I (*A*, *B*, and *C* locus); and class II (*DPA1*, *DPB1*, *DQA1*, *DPB1*, and *DRB1*). We compared the allele frequencies for NPC cases and controls. The study will narrow down to specific variants from the complex *HLA*, which is helpful for immunological studies on investigating the mechanisms of antigen presentation and immune regulations. It will provide more insights for NPC pathogenesis as well as future EBV vaccine development.

Title of Project: A Learning Health System Integrating Clinical and Genomic Information to Enable Early Detection and Early Intervention for Children with Developmental Delay/intellectual Disability

Project No.: NHRI-EX114-11118PI
P.I.: Yann-Jang Chen/陳燕彰
NHRI Researcher: Shih-Feng Tsai/蔡世峯
Key Professional Personnel: Sung-Hui Tseng/曾頌惠, Ming-Lan Tsai 蔡明蘭
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2022 to 2025 (Total: 4 years)

Developmental delay and intellectual disability (DD/ID) affect 5-7% of children. In Taiwan, there is already a government-supported system for screening children with DD/ID and providing early intervention, which includes medical and educational support. However, clinicians often face frustration because a genetic etiologic diagnosis frequently does not lead to therapeutic treatment for children with DD/ID. This can seriously undermine patient trust in science and healthcare. In our project, we aim to establish a nationwide learning health system fostering a continuous learning and improvement cycle. This system will enhance the identification of specific patient groups and the design of optimized management plans for individual patients. Our aims are **Aim 1**: to establish a national network for integrating clinical phenotype, multidisciplinary evaluation data, and genomic information. **Aim 2**: to combine short-read sequencing and long-read sequencing technology for the detection of causative structural variants in DD/ID. **Aim 3**: to achieve patient stratification and personalized management (especially those with epilepsy phenotypes) for DD/ID. **Aim 4**: to investigate the clinical utility of genomic tests for early intervention through health technology assessment. **Aim 5**: to conduct a transethnic comparative genomics study on DD/ID through international collaboration. Till now, we have finished the following.

1. We have established a database platform including all sequencing and phenotypic raw data of all enrolled subjects and provided a user-friendly interface for collecting essential data elements necessary for diagnosing DD/ID.
2. We have used Williams syndrome patients to test long-read sequencing (PacBio) techniques. We have performed WGS analysis for the selected 7 cases, who had negative findings after WES analysis. However, there were still no positive findings. We are now applying the long-read sequencing technique to detect unknown-causing DD/ID patients after short-read WGS from these 7 cases.
3. We have recruited 152 children with DD/ID and performed WES NGS analysis. There are 62 females and 90 males. Their age ranged from 3 months old to 18 years old. About 135 cases have finished WES analysis and the others are ongoing. Positive detection was around 40%.
4. We compared our findings with those reported in the current literature and similar databases. We did not identify any notable ethnic differences or unusual findings in our case. The overall positive detection rate was also comparable, approximately 40–50%. With the accumulation of more cases in the future, clearer conclusions may be drawn.

We will continue to collect DD/ID cases and conduct genetic abnormality analyses. Additionally, we will optimize our database to facilitate reanalysis and integration. At the same time, we will utilize new technologies to improve the detection rate of DD/ID patients and develop new treatment protocols. Some cases of autism may be associated with IGF-1 deficiency or impaired zinc metabolism. In certain individuals, symptoms have significantly improved after adequate zinc supplementation or growth hormone treatment. Therefore, genetic variants related to zinc metabolic pathways may serve as important future research targets. We will also strengthen cooperation with international institutions to advance genomic testing capabilities in Taiwan.

Title of Project: Environmental Co-exposure to Melamine and Phthalates and the Risk of Kidney Injury in Schoolchildren

Project No.: NHRI-EX114-11202PI
P.I.: Ming-Tsang Wu/吳明蒼
NHRI Researcher: Chu-Chih Chen/陳主智
Key Professional Personnel: Hui Ju Tsai/蔡惠如, Chia-Fang Wu/吳佳芳, Yu-Ling Kuo/郭昱伶
Affiliation/Institution: Kaohsiung Medical University
Entire Project Period: From 2023 to 2027 (Total: 5 years)

Background: Chronic kidney disease is an increasing public health concern in Taiwan. Exposure to environmental toxicants such as melamine and phthalates may adversely impact renal health in pregnant mothers and their offspring.

Method: Beginning in October 2012, we initiated the Taiwan Maternal and Infant Cohort Study (TMICS), a multicenter, hospital-based birth cohort. Pregnant women in their third trimester (gestational weeks 29-40) attending routine prenatal examinations at one of nine participating hospitals across Taiwan were invited to enroll. Between 2012 and 2015, a total of 1,433 third-trimester pregnant mothers were successfully recruited, with detailed data collected on personal behaviors, residential environments, and urinary concentrations of 16 xenoestrogens, including melamine, nine phthalate metabolites, nonylphenol (NP), bisphenol A (BPA), and four parabens (methyl- [MP], ethyl- [EP], propyl- [PP], and butylparaben [BP]). From 2016 to 2022, we conducted follow-up assessments on TMICS children, aged 3-7 years, and a total of 552 eligible TMICS children (mean age: 4 years) were successfully recruited with available urinary data for melamine and 11 phthalate metabolites. In this third-year project, we have successfully recruited 590 study children, aged 8-12 years, with 577 available one-spot urine samples for analysis. Biomarkers measured included melamine, cyanuric acid (CYU), 11 phthalate metabolites, five oxidative stress markers (8-OHdG, 8-NO_2-Gua, HNE-MA, 8-isoPGF2α, and MDA), and three early renal injury markers (N-acetyl-β-D-glucosaminidase [NAG], microalbumin, and β2-microglobulin). Spearman correlation analyses were conducted to assess associations among melamine, CYU, oxidative stress biomarkers, and early kidney injury markers in children aged 8-12 years. In addition, linear regression and principal component analysis (PCA) were employed to evaluate associations between xenoestrogen exposures and renal injury markers, as well as potential influencing factors such as maternal behaviors and environmental exposures during pregnancy in third-trimester mothers.

Results: Among the study children aged 8-12 years, urinary analyses were conducted for melamine (n = 261), CYU (n = 573), phthalate metabolites (n = 147), oxidative stress biomarkers (n = 438), and early kidney injury markers (n = 573). Significant positive correlations were observed between urinary concentrations of melamine and CYU with early renal injury biomarkers, including NAG and the albumin-to-creatinine ratio (ACR), as well as with oxidative stress markers. In the analysis of 1,433 third-trimester pregnant mothers, urinary concentrations of BP, MP, BPA, and NP were significantly associated with elevated levels of NAG and ACR, while melamine was significantly associated with NAG. PCA identified two major exposure patterns: one dominated by parabens, which was significantly associated with the use of personal care products (PCPs), and another dominated by phthalates, which was linked to indoor environmental exposures.

Conclusion: In this ongoing study, environmental co-exposure to melamine and CYU among children aged 8-12 years may contribute to early indicators of renal injury. For third-trimester pregnant mothers, reducing the use of PCPs during pregnancy is advised to minimize exposure to endocrine-disrupting chemicals. The study will continue with the analysis of urinary melamine and phthalate metabolite concentrations in study children to further investigate their potential interactive effects on renal health.

Title of Project: Decision Analysis of Care and Prevention of Chronic Kidney Disease : Establish a Model to Support Sustainable Health Goals

Project No.: NHRI-EX114-11208PI

P.I.: Ming Yen Lin/林明彥

NHRI Researcher: Chih-Cheng Hsu/許志成

Key Professional Personnel: Yi-Wen Chiu/邱怡文, Shang-Jyh Hwang/黃尚志, Ping-Hsun Wu/吳秉勳, Cheng-Yin Chung/鍾承穎, Lii-Jia Yang/楊禮嘉, Yihuang Kang/康藝晃, Jeng-Huei Chen/陳政輝, Hsing Luh/陸行

Affiliation/Institution: Kaohsiung Medical University Chung-Ho Memorial Hospital

Entire Project Period: From 2023 to 2026 (Total: 4 years)

Background: The four-year project aims to develop decision support models to assist the government, individuals, and caregivers in making informed decisions to promote a sustainable kidney health system.

Materials and Methods: We estimated 5-year CKD GA state transition matrices and derived parameters of Weibull distributions for transition times using data from Taiwan's universal screening and care programs (2012–2020 and 2012–2021, respectively). The study subjects' time-sequential values of estimated glomerular filtration rate (G1: >90 to G5: <15) and urine dipstick (A1:"− " to A3: "≥1+") or urine albumin creatinine ratio A1 of < 30 mg/dL, A2 of 30–300 mg/dL, and A3 > 300 mg/dL into G1A1 to G5A3 states was integrated. ESKD and death information were obtained from the catastrophic illness and the national death registry databases; the semi-Markov model was applied to simulate a "What if" scenario from a government perspective in which all screening cases were asked to enroll in the P4P care programs. After validating the model, we simulated and compared age- and state-specific average life expectancies.

Results: The study included 4.0 million individuals with 6.1 million CKD state transitions in the screening program and 1.1 million patients with 3.7 million transitions in the care programs. The simulations revealed that participation in care programs increased average life expectancy significantly from 3 to 11 years compared to screening alone. In particular, average life expectancy gains were substantial in younger individuals with advanced CKD states, though diminished progressively with increasing age. The health quality survey shows that health utility scores ranged from 1 (perfect health) to -0.43 (worse than death), with 40% of participants reporting a loss of health utility. Patients with advanced CKD (stages 4, 5, and dialysis) experienced significantly greater health utility loss compared to those in stages 1–2 (differences ranging from 0.37 to 0.55).

Conclusion: The effect of CKD care programs on average life expectancy varies by age and disease state. These findings underscore the importance of identifying factors influencing CKD progression and tailoring state- and age-specific interventions to optimize referral pathways and care delivery. Advanced stages of CKD are significantly associated with a greater loss in health-related quality of life. These findings suggest the need for comprehensive management strategies that go beyond pharmacological treatment to preserve patient health and daily functioning.

Keywords: chronic kidney disease, probability, death, state transition, simulation, life expectancy

Title of Project: Older Volunteers' Competence Assessment and Training for Community-based Long-term Care Services

Project No.: NHRI-EX114-11209PI

P.I.: Kuei-Min Chen/陳桂敏

Key Professional Personnel: Jing-Jy Wang/王靜枝, Li-Hui Lin/林麗惠, Tzu-Yu Lin/林子郁, Meng-Chin Chen/陳孟勤, Chiang-Ching Chang/張江清

Affiliation/Institution: Kaohsiung Medical University

Entire Project Period: From 2023 to 2026 (Total: 4 years)

Background: Older volunteers are the main human resource in community care centers of Taiwan. However, the existing training programs in Taiwan do not specifically address the needs of older volunteers, nor do they provide training for working in the community long-term care service centers. It is crucial to develop a comprehensive training program based on the needs of older volunteers to enhance their knowledge and skills.

Purpose: The 2nd and 3rd years of this project aim to investigate the competencies and needs of older volunteers based on the Older Volunteer Competency Scale (OVCS) developed in the 1st year and to establish its psychometric properties. A training program is developed based on the findings of 2nd year to enhance older volunteers' knowledge and skills.

Methods: The 2nd year employed survey research to assess 1,000 older volunteers' competencies and needs, and to further establish the scale's psychometric properties. In the 3rd year, 10 experts are invited to join the Delphi panel to develop the comprehensive training program for older volunteers in providing community-based long-term care services.

Results: Data of 1,000 participants were randomly divided into two groups for exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). In the first-round EFA, based on the first 500 records of data, the 35 items of the OVCS were classified into three factors and the scale explained 79.4% of the total variance. However, the initial item analysis results did not conform to the results of the literature review, focus group interviews, and the Delphi expert consultations in the 1st year. Consequently, items 4, 12, 13, 28, and 34 were deleted. In the second-round EFA, the 30 items were classified into three dimensions (service awareness, service skills, and interpersonal interaction) and explain 81.6% of the total variance. Afterwards, the CFA was performed using the remained 500 records of data, and the Bollen-Stine bootstrapping method indicated a good model fit with χ^2 / *df* = 2.06, goodness-of-fit index (GFI) = 0.93, root mean square residual (RMR) = 4.59, root mean square error of approximation (RMSEA) = 0.05, adjusted goodness-of-fit index (AGFI) = 0.92, normed fit index (NFI) = 0.96, comparative fit index (CFI) = 0.98, and incremental fit index (IFI) = 0.98. As for the internal consistency and test-retest reliability, the OVCS had a Cronbach's alpha of 0.98 and an ICC of 0.99. The average age of participants was 71.79 ± 4.93 years. The mean scores of the overall scale (3.91 ± 2.66) and the three dimensions were: 3.91 ± 2.85 for service awareness, 4.49 ± 2.76 for service skills, and 3.54 ± 2.86 for interpersonal interaction. The age, volunteering experiences, and educational levels significantly influenced the needs level of older volunteers. We are now in the progress of developing a comprehensive training program based on the needs of older volunteers.

Conclusion: Findings showed that the 30-item OVCS has a strong factor structure and good psychometric properties. The OVCS was used to assess the needs of 1,000 older volunteers, with the goal of informing the design of a tailored training program that could enhance the competencies of older adults in delivering a high-quality, community-based long-term care services.

Title of Project: Scale-out of a Home-based Arm and Hand Exercise Program for Stroke: a Multisite Implementation-efficacy Trial

Project No.: NHRI-EX114-11210PC
P.I.: Chieh-ling Yang/楊婕淩
Key Professional Personnel: Chieh-ling Yang/楊婕淩, Chia-Ling Chen/陳嘉玲, Ching-Yi Wu/吳菁宜, Chih-Hung Chang/張志宏, Jasin Wong/翁嘉遜
Affiliation/Institution: Chang Gung University
Entire Project Period: From 2023 to 2026 (Total: 4 years)

Background: Wrist-worn accelerometers have been used to measure the intensity of upper extremity (UE) practice, but their primary focus is on general arm usage, lacking the ability to capture reaching and grasping of the hand that are relevant for rehabilitation.

Purpose: We aimed to explore the potential of a novel wrist-worn sensor as a meaningful measure for quantifying the amount of reaching and grasping practice during a structured arm and hand exercise session based on the Graded Repetitive Arm Supplementary Program (GRASP) for stroke.

Study Design: A cross-sectional study.

Methods: Fourteen individuals with stroke wore sensor devices (TENZR) on both wrists while performing a structured UE exercise program comprising of 35 exercises. Counts recorded from observation (observed repetitions) and counts from the sensor device (sensor counts) were used to describe the amount of UE practice. The level of agreement between the observed repetitions and sensor counts were examined to determine if the TENZR is a meaningful measure. We also explore if the sensor counts were affected by the level of UE impairment.

Results: The participants performed 792 observed reach and grasp repetitions, with corresponding 711 and 465 sensor counts for the paretic hand and nonparetic hand, respectively, over the hour practice session. The TENZR and the observational method might measure UE movement differently, as evidenced by a lack of agreement between observed repetitions and sensor counts in the paretic hand. No significant relationship between the sensor counts in the paretic hand and the level of impairment was found.

Conclusions: This study used the TENZR to quantify reaching and grasping practice and characterize individual participation pattern for both paretic and nonparetic hands in stroke rehabilitation. The device is an alternative to direct observation for quantifying the intensity of reach-and-grasp practice. In the future, this device could expand to home-based rehabilitation (such home-based GRASP program) and telehealth services, enabling objective monitoring and tracking of UE training progress.

Title of Project: Population-based Molecular Epidemiologic Study of Tuberculosis Transmission in Eastern Taiwan

Project No.: NHRI-EX114-11304PI

P.I.: Chen-Yuan Chiang/江振源

Key Professional Personnel: Lee, Jen-Jyh/李仁智, Lin, Jung-Chun/林榮俊, Lin, Chih-Bin/林智斌, Lo, Hsiu-Yun/羅秀雲, Chu, Chia-Hsiang/朱家祥, Sun, Kuo-Ping/孫國平, Huang, Bei-Cin/黃貝琴, Chen-Yuan Chiang/江振源

Affiliation/Institution: Taipei Medical University

Entire Project Period: From 2024 to 2028 (Total: 5 years)

This population-based molecular epidemiological study plans to perform whole genome sequencing (WGS) for *Mycobacterium tuberculosis* isolates from tuberculosis (TB) patients diagnosed in eastern Taiwan from January 2011 to December 2023 that have been stored at the mycobacterial laboratory of Tzu Chi General Hospital as well as isolates that will be prospectively collected from TB patients notified from 2024-2028. The estimated number of TB isolates collected throughout this 18-year period is about 5,100, representing more than 95% of bacteriologically-confirmed TB cases in 2011-2028 in eastern Taiwan.

This project is the first large-scale population-based study that performs WGS in Taiwan using the Illumina next-generation sequencing platform, a milestone in strengthening the local genomic sequencing capacity of TB. To date, we have performed WGS on 1,242 isolates using the Illumina NovaSeq-6000 platform at the Precision Medicine Research Center, Taipei Medical University. We aim to sequence a total of 2,200 isolates by the end of 2025 and 3,500 isolates by the end of 2026.

From January 2011 to April 2025, a total of 4,131 culture positive TB patients have been notified, including 3,058 (74%) males and 1,073 females. The majority (n = 1,736; 42%) were ≧65 years old, and 1463 (35%) were 45 to 64 years old. WGS of the 1242 isolates generated 150 bp paired-end reads with a mean mapping rate of 98.85%. Drug resistance and lineage were predicted for 1,239 isolates using TB-Profiler. 1,228 patients had both epidemiological and WGS data available, of whom 1,011 (82.3%) were genotypically pan-susceptible, while 217 (17.7%) harbored at least one resistance-conferring mutation.

118 (9.6%) have isoniazid resistance-conferring mutations, in which 64 carried mutations in the fabG1-inhA regulatory region, 5 in the inhA ORF, 61 in katG, and 1 in the oxyR'-ahpC intergenic region. 38 (3.1%) isolates had mutations in rpoB (rifampicin resistance), 32 (2.6%) isolates had mutations in pncA (pyrazinamide resistance), and 27 isolates had mutations in embB and 2 in embA (ethambutol resistance). For lineage distribution, lineage 4 was the most prevalent (n=526, 43%), followed by lineage 2 (n=504, 41%) and lineage 1 (176, 14%).

Overall, this study integrates conventional epidemiological and microbiological data with advanced WGS techniques to provide a comprehensive understanding of the epidemiology and transmission dynamics of TB in eastern Taiwan.

Title of Project: Harnessing Genomic Information in Public Health to Tackle Tuberculosis
Project No.: NHRI-EX114-11305PI
P.I.: Hsien-Ho Lin/林先和
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2028 (Total: 5 years)

Isoniazid-resistant tuberculosis (INH-R TB) is the most common pattern of drug-resistant TB. Compared to pan-susceptible TB (DS-TB), INH-R TB had a higher risk of negative treatment outcome and progression to multidrug-resistant TB. Previous laboratory studies suggested the possibility of reduced risk of transmission of INH-R TB due to fitness cost conferred by the resistance-associated mutations. However, the results from epidemiologic studies were inconsistent with suboptimal study design and limited sample size. We conducted a population-based whole-genome sequencing (WGS) epidemiologic study in Kaohsiung, Taiwan. The study integrated data from routine public health programs, WGS information from M. tuberculosis (M.TB) isolates, and geospatial data.

In this study, WGS was completed in 3,796 of 4,565 (83%) culture-positive TB cases from January 2019 to July 2023. INH-R TB was defined as isolates carrying any INH-resistance-conferring mutations, as identified by the TB-Profiler pipeline. Transmission was defined based on genomic clustering, using a cutoff of 12 single-nucleotide polymorphisms (SNPs) between isolates. Logistic regression was used to analyze the risk of clustering for INH-R TB compared to DS-TB. Besides, we performed sensitivity analyses from different SNPs cutoffs (5 and 10) and different definitions of INH-R TB (genotypic mono-INH-R, genotypic INH-R and Rifampicin susceptible (HrTB), and phenotypic INH-R) to explore the consistency of the relative transmissibility results.

Among the 3,796 sequenced isolates, 336 were identified as INH-R TB and 3,085 were DS-TB. The proportion of cases involved in recent transmission was 16.7% (56/336) for INH-R TB and 20.8% (643/3,085) for DS-TB. After adjusting for sex, age, TB lineage, history of TB, and residential region, INH-R TB was significantly less likely to be genetically clustered than DS-TB (adjusted odds ratio: 0.71; 95% confidence interval (CI): 0.52–0.97). The negative association between INH-R TB and genetic clustering was observed using different definitions of INH-R TB and different SNP cutoffs. The subgroup analysis revealed that the negative association was mainly observed in lineage 2 and not in other TB lineages.

Our findings suggested that INH-R TB was less transmissible than DS-TB, implying a potential fitness cost linked to isoniazid resistance mutations. Further research is needed to elucidate which specific mutations contributed to this reduced fitness and whether compensatory mutations were associated with restored transmissibility. As the collection of TB isolates from Kaohsiung continues through 2028, a larger sample size may reveal additional resistance mutations and provide greater insight into their impact on TB transmission. These efforts will be critical for informing future TB control strategies and understanding the evolutionary dynamics of drug resistance.

Title of Project: Molecular Diagnostics, Prognostics, Pathogenetics, and Therapeutics of *SLC26A4* Variants - A Prevalent Cause of Profound Hearing Impairment in Children
Project No.: NHRI-EX114-11311PI
P.I.: Chen-Chi Wu/吳振吉
Key Professional Personnel: Cheng-Yu Tsai/蔡政育
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Machine Learning Model for Predicting Acute Hearing Loss Episodes in Patients with *SLC26A4* Variants

Background: Pathogenic variants in *SLC26A4* are a major cause of hereditary hearing impairment. Patients with *SLC26A4*-related hearing loss often present with an enlarged vestibular aqueduct (EVA) and incomplete cochlear partition type II (Mondini dysplasia). The hearing patterns are typically progressive and fluctuating, and some patients may experience recurrent episodes of acute hearing loss. Predicting these episodes remains a challenge due to the heterogeneous nature of hearing loss progression. This study utilizes long-term medical data and machine learning techniques to address this gap by modeling and predicting acute hearing deterioration. Through advanced feature engineering and predictive analytics, we aim to improve the early identification of high-risk individuals, facilitating better prevention strategies and personalized clinical management for genetic hearing impairment.

Methods: We included patients diagnosed with EVA and/or carrying pathogenic *SLC26A4* variants. The analysis incorporated demographic data, genotypes, vestibular aqueduct size, presence of Mondini dysplasia, and serial audiograms. A total of 231Taiwanese patients with 1,827 serial audiograms were reviewed. Hearing thresholds at six frequencies (0.25K, 0.5K, 1K, 2K, 4K, and 8K Hz) were analyzed separately for each ear. Acute hearing loss was defined as a deterioration of ≥15 dB at two consecutive frequencies, or ≥30 dB in the average of three consecutive frequencies, occurring within six months between two audiograms. To predict acute hearing loss within the subsequent six months, we analyzed three consecutive audiograms. The data was preprocessed and analyzed in two steps: (1) statistical feature extraction using the ElasticNet model for regression, and (2) time series feature extraction using autoencoders to identify acute hearing loss events. Instead of using raw numerical hearing thresholds, we categorized hearing trends into five groups to extract “shape” features. A five-fold cross-validation approach was applied to validate the models.

Results: A total of 126 patients, comprising 3,267 hearing threshold data points, were included in the analysis. Approximately 81% (102 out of 126) patients experienced acute hearing loss, with 195 events occurring in the left ear and 186 events in the right ear. On average, each individual experienced 1.5 ± 1.8 events of acute hearing loss, with the mean age of occurrence being 8.1 ± 8.7 years. No significant association was found between acute hearing loss and factors such as gender, genotype, vestibular aqueduct size, or the presence of Mondini dysplasia. Our predictive model, utilizing ElasticNet with Categorical Boosting, demonstrated good performance, achieving an area under the curve (AUC) of 0.766.

Conclusions: Our model is capable of predicting the occurrence of acute hearing loss episodes based on the “shape” of the trends of hearing threshold. Predicting acute hearing loss alerts clinicians to closely monitor patients and enables timely interventions.

Title of Project: To Develop and Evaluate a Taiwanese Version of a Comprehensive Self-Management Program for Adults with Irritable Bowel Syndrome

Project No.: NHRI-EX114-11312PC

P.I.: Pei-Lin Yang/楊佩陵

Key Professional Personnel: Tien-Yu Huang/黃天祐, Margaret Heitkemper, Hsuan-Wei Chen/陳宣位, Meei-Shyuan Lee/李美璇, Ya-Jen Chuang/莊雅嫻, Shih-Ming Huang/黃世明

Affiliation/Institution: National Defense Medical Center

Entire Project Period: From 2024 to 2027 (Total: 4 years)

Background: Irritable bowel syndrome (IBS) is a common disorder of brain–gut interaction that significantly affects patients' quality of life. This project aims to develop a culturally appropriate self-management (CSM) intervention for adults with IBS in Taiwan. The first year focused on preparing evaluation questionnaires and assessing stakeholder perspectives on a preliminary CSM intervention.

Purpose: The first year of this four-year mixed-methods project had two primary aims: (1) to translate and validate eight outcome and process measures for future intervention testing; and (2) to evaluate the acceptability, appropriateness, feasibility, and usability of a preliminary CSM intervention for adults with IBS in Taiwan.

Methods: Eight questionnaires were translated and culturally adapted into Traditional Chinese through expert panel review. A convergent mixed methods study was then conducted with 17 patients diagnosed with Rome IV-defined IBS and 17 healthcare providers experienced in IBS care, recruited from secondary and tertiary healthcare settings in Taiwan. Data collection included the translated questionnaires and semi-structured interviews. Quantitative data were analyzed using descriptive statistics, while qualitative data were analyzed using thematic analysis.

Results: Five outcome and process measures (i.e. symptom severity, work and activity productivity, visceral sensitivity, self-efficacy, self-regulation) and implementation outcomes (acceptability, feasibility, appropriateness, usability) were translated and validated. Patients reported high acceptability (M = 17.6 out of 20) and appropriateness (M = 17.2 out of 20); providers reported similar scores (M = 17.6 and 16.5, respectively). Feasibility ratings were also high (M =17.8 out of 20) in both groups. Usability scores (scale range 0-100) averaged 62.2 for patients and 58.5 for providers. Qualitative interviews supported these findings, describing the intervention as comprehensive and relevant, particularly for nutrition and mental health. Key challenges included low awareness of the gut–brain connection, limited time, and barriers to interdisciplinary care. Most patients reported prior experience with Traditional Chinese Medicine (TCM) and supported its inclusion (e.g., dietary principles, mind–body practices), though provider views remained mixed.

Conclusion: This initial phase produced validated outcome measures and stakeholder insights into a preliminary CSM intervention for IBS in Taiwan. These findings are guiding active refinements to enhance the intervention's content and delivery, with particular emphasis on adapting the nutritional components based on Taiwanese dietary guidelines. The potential integration of TCM elements will also be further explored based on feasibility and available evidence. These efforts will support the formal adaptation and pilot testing planned for Years 2–4.

Keywords: Irritable Bowel Syndrome, Brain–Gut Interaction, Self-Management, Cultural Adaptation

Title of Project: Uncovering Genetic Diversity of Austronesian Ancestry for Advancing Precision Medicine and Health Equity of the Indigenous People of Taiwan

Project No.: NHRI-EX114-11331PI

P.I.: Wen-Ya Ko/可文亞

Key Professional Personnel: Chao-Kuang Lin/林昭光、Valis Tanapima/田知學、Jian-Lian Chen/陳淨蓮、Mei-Ling Kang/康梅鈴

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2024 to 2026 (Total: 3 years)

Genetic diversity plays a fundamental role in medicine, influencing disease susceptibility, drug response, diagnostic accuracy, and the implementation of precision medicine. In Taiwan, several government-funded biobank initiatives aim to comprehensively catalog the genetic variants associated with disease risk. However, the current whole-genome genotyping arrays employed by the Taiwan Biobank are primarily designed for individuals of Han Chinese ancestry. To ensure that precision medicine benefits all citizens, including those of Austronesian descent, it is essential to incorporate genetic variants unique to Taiwan's Indigenous populations. In this study, we analyzed genome-wide SNP array data comprising 752,921 markers from 1,119 individuals representing seven Indigenous tribes of Taiwan including Amis, Atayal, Bunun, Paiwan, Puyuma, Rukai, and Truku. Our preliminary findings reveal that the genetic structure of Taiwan's Indigenous peoples is clearly distinct from those of Han Taiwanese, with substantial differentiation observed between Indigenous groups. Furthermore, by examining the length distribution of linkage-disequilibrium blocks, we identified genomic regions exhibiting signatures of incomplete positive selection in each population. Notably, the landscapes of positive selection vary across Indigenous groups, highlighting the population-specific nature of recent adaptive events. In particular, indigenous populations inhabiting the plains and coastal regions exhibited stronger signals of positive selection at the *HLA* loci than those residing in mountainous areas. Our findings underscore the importance of including Indigenous genomic data in national biobank efforts. Future research will prioritize whole-genome sequencing of these populations to achieve a more comprehensive representation of genetic diversity in Taiwan. Such efforts will enable biomedical studies and healthcare strategies to more equitably address the distinct evolutionary histories and health needs of all communities.

Title of Project: Development, Validation, and Prospective Clinical Trial of a Tool for Predicting Serious Adverse Events in Return Emergency Department Visits
Project No.: NHRI-EX114-11332PI
P.I.: Chu-Lin Tsai/蔡居霖
Key Professional Personnel: Chien-Hua Huang/黃建華、Fu, Li-Chen/傅立成
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Deep Learning–Based Model with Static and Dynamic Features to Predict Emergency Department Revisit: Development and Validation Study

Su-Yin Hsu, Jhe-Yi Jhu, Jun-Wan Gao, Chia-Hsin Ko, Chien-Hua Huang, MD,
Li-Chen Fu, Chu-Lin Tsai,

Background: Emergency department (ED) revisit prediction is a critical issue in the medical domain. Accurately forecasting the likelihood of patient revisits to the ED can provide valuable decision support for attending physicians when making discharge decisions. Among all revisit cases, identifying high-risk revisits (revisits with intensive care unit admissions, cardiac arrest, or requiring emergency surgery) is especially crucial, as they may indicate deficiencies in initial emergency care. Although several machine learning models have been proposed for predicting ED revisits, to date, no deep learning-based models have been developed specifically for this task.

Methods: We designed a data preprocessing strategy to address the irregularity of dynamic feature time series and developed a time-aware modeling framework that integrates both static and short-term temporal features. We proposed a hybrid model that is composed of temporal convolutional network (TCN) and feature tokenizer (FT)-Transformer. By constructing a hybrid architecture, our model captures a more comprehensive representation of patient status, enhancing early identification of potential ED revisiting cases and overcoming the limitations of models that rely solely on static features.

Results: We utilized ED data from National Taiwan University Hospital (NTUH) across various periods. First, we used the NTUH dataset from 2016 to 2019 to evaluate the model. Our model achieved an area under the receiver operating characteristic curve (AUROC) of 0.8453 and an area under the precision-recall curve (AUPRC) of 0.0935 in the high-risk revisit prediction task, as well as an AUROC of 0.7250 and an AUPRC of 0.2005 in the general revisit prediction task. We also utilized the emergency department dataset from NTUH spanning 2020 to 2022 as our internal validation cohort. Our model achieved an AUROC of 0.7976 and an AUPRC of 0.0103 for the high-risk revisit prediction task (base rate = 0.002) and an AUROC of 0.7300 and an AUPRC of 0.1537 for the general revisit prediction task (base rate = 0.05). Both results significantly outperformed the static-only logistic regression baseline. The AUPRC has increased from 0.006 to 0.0103 in predicting high-risk revisits. Additionally, we performed feature importance analysis, demonstrating that the heart rate influences the prediction results the most. Also, we conducted case studies to identify key patient characteristics that contributed to the model's predictions.

Conclusions: The results demonstrate that our model effectively integrates dynamic time-series and static tabular features, yielding reliable performance in predicting emergency department revisits. This highlights the potential of fusing different types of clinical data sources to improve early risk identification. Our findings suggest that time-aware, hybrid deep learning architectures can serve as a valuable tool in clinical decision-making.

Title of Project: Outcomes of Mirror Therapy Preceding Augmented Reality in Stroke Rehabilitation
Project No.: NHRI-EX114-11333PI
P.I.: Keh-chung Lin/林克忠
Key Professional Personnel: Wen-Shiang Chen/陳文翔, Chia-Ling Chen/陳嘉玲, Ya-Ju Chang/張雅如, Ya-Yun Lee/李亞芸, Grace Yao/姚開屏, Yi-Shiung Horng/洪怡珣, Wan-Ling Hsu/徐宛玲, Yi-Hsuan Wu/巫怡萱, Hsiao-Chieh Pan/潘曉潔
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Background: Mirror therapy (MT) and augmented reality (AR) are gaining popularity in stroke rehabilitation. MT uses mirror visual feedback to promote bilateral brain coupling and increase primary motor cortex excitability. AR offers an interactive context of practice for promoting motor and cognitive recovery. MT and AR may complement each other for hybrid interventions in stroke rehabilitation. This study investigated the benefits of MT-primed AR (MT+AR) versus AR group, relative to conventional therapy (CT) for individuals with stroke. The MT-primed AR and AR alone were hypothesized to render better outcomes than the CT and show the differential benefits.

Method: The study randomly assigned 44 stroke survivors to the MT+AR group, the AR, or the CT group. Each treatment session was 90 minutes, 3 times a week, for 6 weeks. All assessments were administered before, immediately after treatment, and at 3 months. Primary outcome measures were the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) and the Berg Balance Scale (BBS). Secondary outcome measures were the revised Nottingham Sensory Assessment (rNSA), Chedoke Arm and Hand Activity Inventory (CAHAI), Motor Activity Log (MAL), and Stroke Impact Scale Version 3.0 (SIS). Adverse events were monitored before and after each session.

Results: After 6 weeks of treatment, all groups demonstrated significant improvements in the FMA-UE, BBS, CAHAI, MAL, and SIS. In the between-group comparisons, MT+AR and AR groups demonstrated significant advantages in the BBS, proprioception scale of rNSA and SIS, compared with the CT group. Only the MT+AR group, not the AR group, showed significantly better improvements in the FMA-UE and tactile scale of rNSA than the CT group. The MT+AR and AR alone showed differential benefits in the FMA-UE, tactile scale of rNSA, and SIS; the MT+AR rendered significantly better benefits. There were no significant differences among the three groups in the stereognosis scale of rNSA and MAL. No adverse effects were observed.

Conclusion: MT+AR and AR both improved sensorimotor function, balance, task performance, and quality of life in stroke patients with moderate to severe motor impairments. Compared to CT, both were more effective for enhancing balance, mobility, proprioception, and quality of life. MT+AR showed greater benefits than AR in upper limb motor function, tactile sensation, and overall quality of life. Therapists should tailor interventions based on patient goals.

Keywords: Stroke, Mirror therapy, Augmented reality, Gamification, Combinatory regimen

Title: COVID-19 Pandemic: Examining the Relationship Between Excess Mortality and Containment Strategies Across 34 Countries

P.I.: Hsiao-Hui Tsou/鄒小蕙

Presenter: 成捷

Institute/Center: National Health Research Institutes

This study expands the application of COVID-19 containment performance indicators to evaluate their association with excess mortality across countries. We conducted a longitudinal analysis encompassing 34 countries from 2020 to 2022, integrating data on excess mortality, containment performance, and relevant structural factors.

The average excess mortality ratio among these countries was 1.09 in 2020, 1.14 in 2021, and 1.11 in 2022. Thirteen countries exhibited a consistent year-on-year increase in excess mortality, while another thirteen showed an increase from 2020 to 2021 followed by a decline in 2022. Six countries experienced a decrease between 2020 and 2021 but saw a subsequent increase in 2022. Only two countries demonstrated a continuous annual decline over the three-year period. For countries with top containment performance compared with bottom performance, excess deaths were reduced by 5.75% (95%CI, -0.1, -0.01; P =0.02) and 12.85% (95%CI, -0.17, -0.08; P < 0.0001) in 2020 and 2021, respectively. For countries with middle containment performance compared with bottom performance, excess deaths were reduced by 6.66% (95%CI, -0.11, -0.02; P =0.01) and 10.56% (95%CI, -0.15, -0.06; P < 0.0001) in 2020 and 2021, respectively.

These findings emphasize a consistent association between stronger containment performance and reduced excess mortality, particularly during the initial and vaccine deployment phases of the pandemic.

Our study covers the early phase of the pandemic, the vaccine development period, and the post-pandemic phase, allowing for a more comprehensive understanding of how excess mortality and government responses evolved across different stages. The findings offer valuable insights for future policy development in response to emerging infectious diseases. Furthermore, our results underscore the need for new and adaptive indicators in the post-pandemic era. As lifestyles and societal norms shift, these indicators must reflect a balanced approach—ensuring continued protection against infectious threats while safeguarding mental and physical well-being, promoting social and economic stability, and supporting sustainable development.

Title : Establishing and Using Threshold of Surrogate Endpoint in Relation to Clinical Endpoint

P.I. Name : Hsiao-Hui Sophie Tsou/鄒小蕙
Presenter : Yu-Chieh Cheng/鄭宇傑
Institute/Center : National Health Research Institutes

Clinical trials are a cornerstone of drug development, providing essential evidence for evaluating the safety and efficacy of new treatments. Among the outcome measures used in such trials, clinical endpoints reflect direct health benefits, such as survival or disease remission. While these endpoints are considered definitive, they often require long follow-up periods and large sample sizes, resulting in high costs and time consumption. To address these challenges, surrogate endpoints—biological markers or intermediate outcomes that predict clinical effects—are frequently used as more efficient alternatives. The use of surrogate endpoints introduces complexity. Even when a linear relationship exists between a surrogate and the true clinical endpoint, it is still necessary to identify a threshold value of the surrogate that signifies a meaningful clinical benefit. Determining this threshold involves understanding the joint statistical distribution of the surrogate and clinical outcomes, which includes several parameters and inherent uncertainties. In this study, we propose the concept of a “working threshold,” which incorporates statistical uncertainty into the threshold estimation process. This approach aims to improve the interpretability and practical application of surrogate endpoints, especially in settings where data are limited or variability is high.

Title : Unlocking Rapid Detection: Predominant Azole-resistant Genotypes in *Candida tropicalis*

P.I.: Hsiu-Jung Lo/羅秀容
Presenter : Kuo-Yun Tseng/曾國鋆
Institute/Center : National Health Research Institutes

The Taiwan Surveillance of Antimicrobial Resistance of Yeasts (TSARY), initiated in 1999 and conducted every four years, has identified *Candida tropicalis* as a major cause of non-albicans candidemia, with a notably higher resistance rate to fluconazole compared to other *Candida* species. Importantly, fluconazole-resistant *C. tropicalis* isolates also show cross-resistance to other azoles. Moreover, clade 4 is the predominant azole-resistant genotype (90.2%) among 92 isolates. In addition, of the 334 *C. tropicalis* isolates collected from TSARY 2022, most of the clade 4 isolates were resistant to azole (32/36). The primary resistance mechanism in clade 4 *C. tropicalis* is overexpressing mutated *ERG11*, the azole target. This study aims to develop methods for the rapid identification of the predominant azole-resistant *C. tropicalis* genotype. Our genomic analysis revealed that the sequences of CTRG_05978 and *SNQ2* are strongly linked to the clade 4 genotype. Additionally, we established a comprehensive surveillance method using multiplex PCR targeting nine genes, followed by MinION sequencing. By optimizing annealing temperature, extension length, and primer set amounts, we developed a protocol enabling the simultaneous processing of 96 samples in a 96-well plate. We also created a program for automatic assignment of diploid sequencing types, ensuring accurate and efficient routine molecular typing. Overall, this study offers significant advancements in the diagnosis and management of drug-resistant fungal infections, highlighting its potential impact on clinical practices.