2026 Biomedical Research Symposium of National Health Research Institutes

115 年度國家衛生研究院生物醫學學術研討會

Program Book

August 5 - 6, 2026

※ 本摘要集內容請勿擅自引用 ※

National Health Research Institutes, Taiwan

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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
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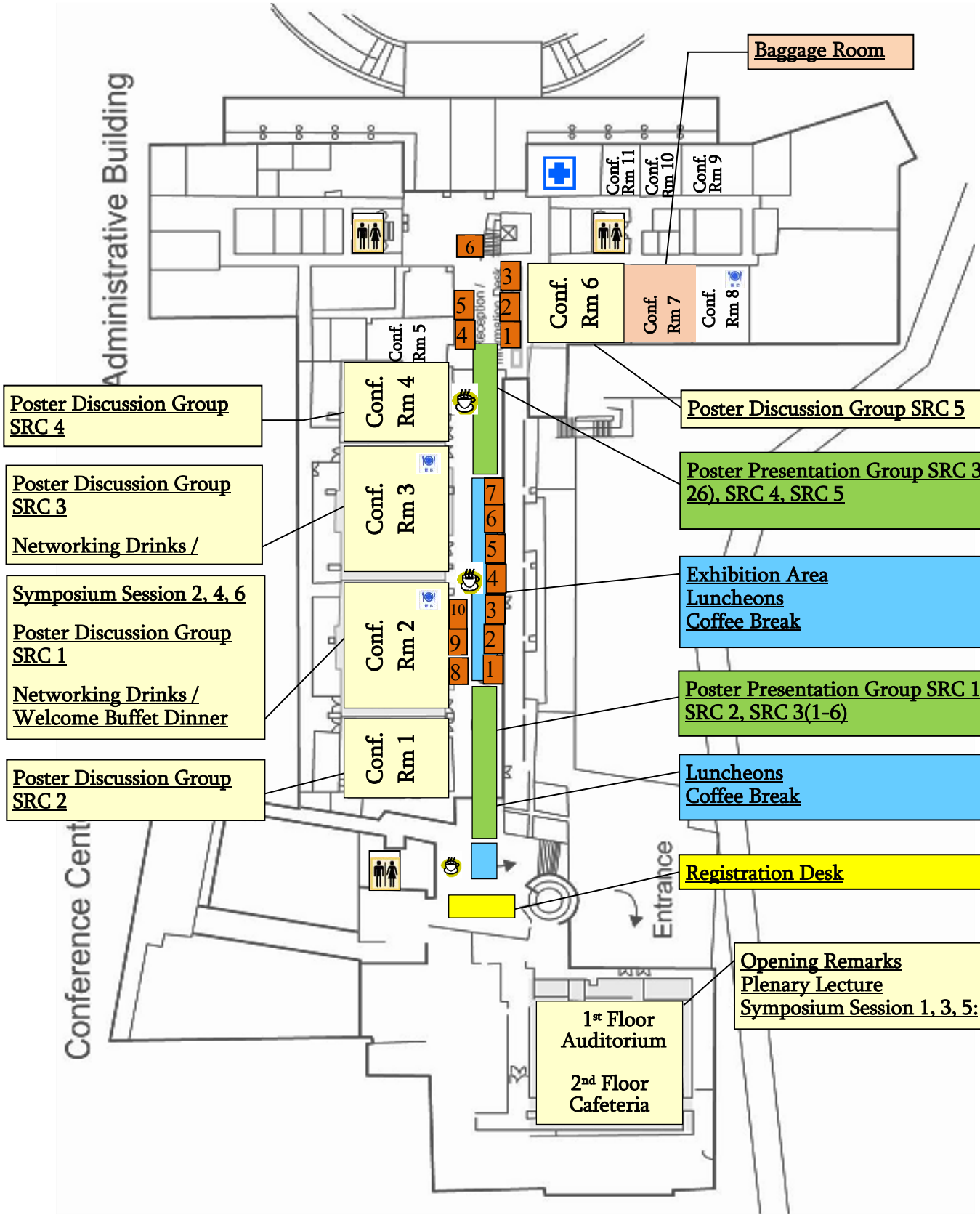
115 年度國家衛生研究院生物醫學學術研討會

2026 Biomedical Research Symposium of National Health Research Institutes

會場分佈圖 (Floor Plan)



115 年度國家衛生研究院生物醫學學術研討會
2026 Biomedical Research Symposium of National Health Research Institutes

Daily Program

August 5（Wednesday）

Last updated：July 20, 2026

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 **The Oncogenic RNA Complexes of Oral Cancer** *Dr. Hsing-Jien Kung* 龔行健院士 Taipei Medical University 臺北醫學大學/ Academia Sinica 中央研究院	
11:00-11:20	**Coffee Break**	
	Symposium Session 1 : 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 2 : Medical Engineering** **(Venue : Conference Room 2)** Chairpersons: *Dr. Kai-nan An* 安介南院士 Mayo Clinic College of Medicine *Dr. Chii-Wann Lin* 林啟萬特聘研究員 National Health Research Institutes 國家衛生研究院
11:20-11:45	**How Early *KRAS*-Mutated Pancreatic Cells Escape Oncogene-Induced Senescence and Immune Surveillance** *Dr. Shaw-Jeng Sean Tsai* 蔡少正講座教授 National Chung Cheng University/ National Cheng Kung University 國立中正大學/國立成功大學	**Translational Development of a Handheld Multiparametric PS-OCTA System for *In Vivo* 5D Optical Biopsy and Early Oral Oncology** *Dr. Wen-Chuan Kuo* 郭文娟教授 National Yang Ming Chiao Tung University 國立陽明交通大學

11:45-12:10	**How do Cancer Cells Get their Fats?** *Dr. Tien Hsu* 徐洏講座教授 China Medical University 中國醫藥大學	**Cold Atmospheric Plasma-Reinforced Micro/Nano-Biomimicked Hybrid Carrier Loaded with Platelet Lysate for Enhanced Osteoarthritis Attenuation** *Dr. Er-Yuan Chuang* 莊爾元教授 Taipei Medical University 臺北醫學大學
12:10-12:35	**Decoding Lethal Prostate Cancer: Urinary Biomarkers and the Functional Role of Pericellular Serine Proteases** *Dr. Ming-Shyue Lee* 李明學教授 National Taiwan University 國立臺灣大學	**3D-Printed Intervertebral Cages for rhTMD2/3 delivery to Enhanced Implant Stability and Spinal Fusion** *Dr. Yan-Jye Shyong* 熊彥傑副教授 National Cheng Kung University 國立成功大學
12:35-13:00	**Vulnerable Therapeutic Targets in ARID1A-Deficient Pancreatic Cancer** *Dr. Wen-Chun Hung* 洪文俊特聘研究員 National Health Research Institutes 國家衛生研究院	**Advanced Sensing Technologies and Progress in Organoid Applications** *Dr. Chii-Wann Lin* 林啟萬特聘研究員 National Health Research Institutes 國家衛生研究院
13:00-14:00	**Lunch**	

	Symposium Session 3 : 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 4 : 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	**Poster Discussion (Venue: Conference Room 4)** Chairperson: *Dr. Kai-nan An* 安介南院士 Mayo Clinic College of Medicine
14:00-14:25	**Mechanisms underlying B Cell Differentiation and Antibody-Mediated Protection** *Dr. Kuo-I Lin* 林國儀特聘研究員 Academia Sinica 中央研究院	**Developing Neuronavigation-Guided Focused Ultrasound for Brain Therapy: From Concept to Clinical Trials** *Dr. Kuo-Chen Wei* 魏國珍教授/主治醫師 Chang Gung Medical Foundation 長庚醫療財團法人	**Group SRC4 - Medical Engineering**

14:25-14:50	**Opposing function of USP5 in MRE11 endonuclease activity to evade anti-tumor immunity** *Dr. Shao-Chun Wang* 王紹椿教授 China Medical University 中國醫藥大學	**Sertm2 Is A Conserved Micropeptide that Promotes GDNF-mediated Motor Neuron Subtype Specification** *Dr. Jun-An Chen* 陳俊安研究員 Academia Sinica 中央研究院
14:50-15:15	**MedSelect: A Tumor-Microenvironment-on-Chip Platform for Functional Immunotherapy Screening and Translational Oncology** *Dr. Jen-Huang Huang* 黃振煌副教授 National Tsing Hua University 國立清華大學	**Toward Precision Neuromodulation in Epilepsy: Mapping and Modulating the Epileptogenic Network** *Dr. Hsiang-Yu Yu* 尤香玉主治醫師 Taipei Veterans General Hospital 臺北榮民總醫院
15:15-15:40	**Focal Adhesions in Human Diseases** *Dr. Su Hao Lo* 羅世皓特聘研究員 National Health Research Institutes 國家衛生研究院	**APOE4 and the Failure of Brain Resilience in Alzheimer's Disease** *Dr. Feng-Shiun Shie* 謝奉勳研究員 National Health Research Institutes 國家衛生研究院
15:40-16:00	**Coffee Break**	
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17:00-17:30	**Networking Drinks**	
17:30-19:00	**Welcome Buffet Dinner**	

August 6 (Thursday)

Last updated：July 20, 2026

09:00-09:50	**Plenary Lecture (Venue : Auditorium)** Chairperson: *Dr. Huey-Kang Sytwu* 司徒惠康院長 National Health Research Institutes 國家衛生研究院 **Centrosome and Ciliary Biology in Neurodevelopmental Disorders and Cancer** *Dr. Tang K. Tang* 唐堂院士 Academia Sinica 中央研究院	
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 : Clinical and Public Health (Venue : Conference Room 2)** Chairpersons: *Dr. C. Kent Kwoh* 郭堅教授 University of Arizona Arthritis Center *Dr. Chih-Cheng Hsu* 許志成研究員 National Health Research Institutes 國家衛生研究院
11:00-11:25	**The Pulse of Life: From Sinoatrial Node Pathogenesis to Biological Pacing** *Dr. Yu Feng Hu* 胡瑜峰教授 National Yang Ming Chiao Tung University 國立陽明交通大學	**Plastic Pollution and Kidney Health: From RAPIT to TMICS and Beyond** *Dr. Ming-Tsang Wu* 吳明蒼特聘教授 Kaohsiung Medical University 高雄醫學大學
11:25-11:50	**Organelle Patch-Clamp Approaches to Study Endolysosomal Ion Channels in Disease** *Dr. Cheng-Chang Chen* 陳政彰助理教授 National Taiwan University 國立臺灣大學	**Old Problems, New Solutions: How AI is Changing Today's ER** *Dr. Chu-Lin Tsai* 蔡居霖臨床副教授 National Taiwan University 國立臺灣大學

11:50-12:15	**Translating Urine Metabolomics into Diagnostics: Isobutyric Acid and Valine as Early Pathogenic Biomarkers for Pediatric Steatotic Liver Disease** *Dr. Chun-Mei Hu* 胡春美助研究員 Academia Sinica 中央研究院	**Advancing Taiwan Kidney Care: Learning from Real-World Evidence** *Dr. Ming Yen Lin* 林明彥醫學副研究員 Kaohsiung Medical University 高雄醫學大學
12:15-12:40	**Making RNA circular: Wrapping the Messenger in a Closed RNA** *Dr. Chia-Yi Yu* 余佳益副研究員 National Health Research Institutes 國家衛生研究院	**Challenges of Youth-onset Type 2 Diabetes in Taiwan** *Dr. Chih-Cheng Hsu* 許志成研究員 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. Kai-nan An* 安介南院士 Mayo Clinic College of Medicine **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	

2026 Biomedical Research Symposium of National Health Research Institutes
- Plenary Speakers-

Dr. Hsing-Jien Kung, Taipei Medical University / Academia Sinica

Dr. Tang K. Tang, Academia Sinica

Hsing-Jien Kung, Ph.D.

Chair Professor, Taipei Medical University

Academician, Academia Sinica
President Emeritus, NHRI
Distinguished Professor Emeritus, UC Davis

Education

1965-1969	B.S. Chemistry, National Taiwan University
1970-1975	Ph.D. Chemistry, California Institute of Technology

Research and Professional Positions Held in Chronological Sequence

1975-1976	Lieutenant Tactical Control and Liaison Officer, Commander General of Missile Corps, Taiwan
1976-1978	Postdoc, Microbiology, UC San Francisco
1978-1982	Assistant Professor, Department of Biochemistry, Michigan State University
1982-1984	Associate Professor, Department of Biochemistry, Michigan State University
1984-1988	Associate Professor, Dept. of Molecular Biology & Microbiology, CWRU School of Medicine
1988-1998	Professor, Dept. of Molecular Biology & Microbiology, CWRU School of Medicine
1989-1998	Professor, Department of Medicine, Case Western Reserve University School of Medicine
1990-1998	Associate Director of Basic Science, CWRU Cancer Center
1998- 2012	Professor, Dept. Biochemistry and Molecular Medicine, UC Davis, School of Medicine
1998-2018	Deputy Director and Director of Basic Research, UC Davis Cancer Center
2008- 2018	Distinguished Professor, Dept. Biochemistry and Molecular Medicine, UC Davis, School of Medicine
2012-2015	President, National Health Research Institutes, Taiwan

Research Interests

My lab has contributed to our understanding of oncogenes, signal transduction, viral oncogenesis, cancer metabolism and epigenetics. We were credited for the original discovery of dimer structure of retrovirus genome (Cell, 1976), erbB/EGFR as a target gene for retroviral insertion (Cell, 1983, 1986, 1993, Nature, 1981), establishing this locus as a protooncogene, initial cloning of human c-src gene and demonstrating oncogenicity of v-src DNA (PNAS, 1983), and the discoveries of several tyrosine kinase- and viral oncogenes (Nature Cell Biol, 2002, PNAS, 1992, 1998). In the area of prostate cancer, his lab contributed to: the first tyrosine kinase profile (PNAS, 1996) , the discovery of truncated AR in CWR22Rv1 (Cancer Res, 2002, 2009), the discovery of IL6 and erbB crosstalk (Nature, 1998), the demonstration of IL6-induced neuroendocrine differentiation (PNAS, 1998), the identification of the first Long-noncoding RNA coactivator of myc (PNAS, 2014) and of HIF-1a (Nat Comm, 2017), the definition of the origin of human retrovirus XMRV (dispelling its

involvement in prostate cancer) (Science, 2012) , the first demonstration of tumor specific killing of prostate cancer by arginine-deprivation (Cancer Res, 2009), the discovery of chromatin-autophagy (PNAS, 2014), histone demethylase KDM4A as E2F coactivator and tumor metabolism (Cell Reports, 2016), arginine deprivation leads to cGAS-STING activation (Theranostics, 2021), arginine as an epigenetic regulator of mitochondria (Nature Communication, 2021, Cell Reports, 2023) and PKM2 as a metabolic oncogene (Nature Communication, 2024, Advanced Science, 2025)

My current interests are :1) Metabolic modulation of ferroptosis to overcome prostate cancer drug resistance. 2) Super-enhancers involved in prostate cancer progression. 3) RNA complexes associated with hypoxia and hybrid EMT responses. 4) Exosomal RNAs involved in muscle aging and sarcopenia.

I was the founding Associate Director of Basic Science of Case Western Reserve University Cancer Center and of UC Davis Cancer Center. I have served in numerous NCI and DOD review panels including OIA, SPORE and PPG study sections. I served as a member of several Cancer Center External Advisory Boards, including those of UC Irvine Chao Family Cancer Center, City of Hope, and Oregon Health and Science Institute Knight Cancer Center. I also served as a member of international advisory boards including UCLA Prostate Cancer SPORE.

Major Honors and Awards

1983-1987	Faculty Research Award, American Cancer Society
1998-present	Academician of the Academia Sinica, ROC
2005	UC Davis School of Medicine Faculty Research Award
	Goodman-Blum Professor in Cancer Research, CWRU
	Honorary Distinguished Fellow, NHRI, Taiwan
2006	Joan Oettinger Memorial Award in Lung and Cancer Research
2006	Society of American Asian Scientists in Cancer Research (SAASCR), recipient of annual award
2007	Auburn Community Cancer Endowment Chair in Basic Science, UC Davis
2010-present	Tang Prize Executive Committee Member
	0.05% Top Scientists world ranking in ScholarGPS Cancer cell
	NCI Merit Award (CA39207)
	NCI Merit Award (CA46613)
2012	NIH Norman Salzman Lectureship
2018-2022	Gordon Conference on Personalized Medicine, Chair and Vice Chair
	Honorary Research Fellow, NHRI
	Life-Time Distinguished Professor, NTHU
2019	Keystone Symposia “Innate Immune Receptors: Roles in Immunology and Beyond”, co-organizer
2022-2024	Keystone Symposia “Inflammation, microbiota and cancer”, co-organizer
2024	National Taiwan University Outstanding Alumnus

The Oncogenic RNA Complexes of Oral Cancer

Hsing-Jien Kung
龔行健

College of Medical Science and Technology
Taipei Medical University, Taiwan

In this presentation , I shall discuss two novel oncogenic RNA complexes associated with the progression of head and neck squamous cell carcinoma (HNSCC). HNSCC is among the most common cancers in the world, and oral squamous cell carcinoma (OSCC) represents the major type of HNSCC. Despite the intensive efforts to identify therapy for OSCC over the past few years, the patient's survival was not significantly improved. EMT (epithelial-mesenchymal transition) is the principal driving force for metastasis and remains a conundrum. It is now well recognized that EMT is not a binary process and may go through several steps, characterized by partial EMT (pEMT). We have uncovered a transcriptional complex organized by a long noncoding RNA as a key regulator of EMT and pEMT processes including collective migration. Oral cancer is often locally aggressive with bulky tumor, displaying hypoxia features and requires HIF-1α for its survival and progression. A second RNA complex we identified involves an antisense RNA which serves as a key connector of PKM2 and HIF-1α. This RNA complex reshapes HIF-1α chromatin binding landscape and orchestrates the hypoxia and metabolic responses. Our studies provide new therapeutic targets for intervention. The work represents a close collaboration between TMU, NHRI, NYCU and NTHU with support from NSTC

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Education

1974-1978	B.S., Department of Biology, Tunghai University, Taiwan
1981-1983	M.S., Institute of Microbiology and Immunology, National Yang Ming University, Taiwan
1984-1986	M.Ph., Department of Human Genetics, Yale University, U.S.A.
1984-1988	Ph.D., Department of Human Genetics, Yale University, U.S.A.

Research and Professional Positions Held in Chronological Sequence

1987-1988	Teaching Assistant, Department of Human Genetics, Yale University, U.S.A.
1988-1989	Postdoctoral Fellow, Department of Medicine, Yale University, U.S.A.
1989-1995	Associate Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan
1995-2010	Full Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan
2010-present	Distinguished Research Fellow, Institute of Biomedical Sciences Academia Sinica
1997-1999	Deputy Director, Institute of Biomedical Sciences, Academia Sinica
2004-2006	Deputy Executive Secretary, The Central Advisory Committee, Academia Sinica
2006-2007	Executive Secretary, The Central Advisory Committee, Academia Sinica
2008-2009	Director, Advisory Office, Ministry of Education, ROC
2022-2026/6	Vice President, Academia Sinica

Research Interests

1. Cell Biology; Neuroscience; Cancer Biology
2. Centrosome/Cilia Biology and Related Human Diseases

Cell division in higher animals requires coordinated DNA replication and centriole duplication. While DNA replication has been extensively characterized, the molecular mechanisms governing centriole biogenesis remain incompletely understood. Centrioles are essential for centrosome function, ciliogenesis, and mitotic spindle organization. Defects in centrosome-associated proteins are strongly linked to primary microcephaly (MCPH), a neurodevelopmental disorder characterized by reduced brain size and intellectual disability.

Dr. Tang's laboratory has made major contributions to elucidating the molecular mechanisms of centriole duplication and their roles in human disease. His group first identified the centrosomal proteins STIL (EMBO J, 2011), CEP135 (EMBO J, 2013), and RTTN (Nat Commun, 2017) as associated partners of CPAP, forming functional complexes that regulate distinct stages of centriole assembly and elongation. Importantly, mutations in CPAP, STIL, CEP135, and RTTN are associated with MCPH. Using mouse and brain organoid models, his lab found that defects in the CPAP gene lead to neuronal cell death, premature neuronal differentiation, and severe brain developmental defects, supporting the hypothesis that impaired centriole replication disrupts cortical neurogenesis and causes microcephaly (J Cell Sci 2020; Front Cell Dev Biol, 2022).

His laboratory further demonstrated that CPAP (Nat Cell Biol 2009) and CEP120 (J Cell Biol 2013) regulate centriole elongation, and reveal the mysterious role of ciliogenic role of CEP120 in Joubert Syndrome, a congenital cerebellar disorder (Genes & Dev 2022). In addition to this, his lab also found that myosin-Va-mediated transportation of preciliary vesicle to the mother centriole is the earliest event that defines the onset of ciliogenesis (Nat Cell Biol 2018). In cancer research, his lab found that STIL overexpression can induce centriole amplification, genomic instability, and FOXM1-mediated oncogenic signaling (J Biomed Sci 2022). Future studies will combine molecular, genetic, mouse, and human brain organoid approaches to investigate centrosome-related neurodevelopmental disorders and cancer.

Major Honors and Awards

1992, 1995, 1998	The Outstanding Research Award, NSTC
2010, 2015, 2020	Academia Sinica Investigator Award
2011	The Phi Tau Phi Scholastic Honor Society Member
2014	Wang, Ming-Lin Outstanding Research Award
2014	The Ministry of Education Academic Award
2022	Academician, Academia Sinica

Centrosome and Ciliary Biology in Neurodevelopmental Disorders and Cancer

Tang K. Tang
唐堂

Institute of Biomedical Sciences, Academia Sinica, Taiwan

Cell division in higher animals requires coordinated DNA replication and centriole duplication. While DNA replication has been extensively characterized, the molecular mechanisms governing centrosome duplication remain incompletely understood. The centrosome is the primary microtubule organizing center (MTOC), composed of two centrioles and the pericentriolar material (PCM) surrounding them. In vertebrates, the centriole consists of nine triplets of microtubules, essential for the formation of dynamic microtubule arrays, mitotic spindles, cilia, and flagella. Centrosome abnormalities are thought to be associated with aneuploidy, cancer, and microcephaly, while ciliary defects are associated with a range of diseases collectively known as ciliopathies, including retinal degeneration, polycystic kidney disease, and Joubert syndrome. Primary microcephaly (MCPH) is a neurodevelopmental disorder characterized by small brain size and mild to severe intellectual disability. Interestingly, mutations in many centrosome genes have been reported to cause MCPH, and overexpression of these genes can lead to tumors. Over the past 20 years, my lab has identified several key proteins involved in centriole duplication and cilia formation, including CPAP (Nat Cell Biol 2009, Cell Rep 2016, J Cell Sci 2020, Front Cell Dev Biol 2022), STIL (EMBO J 2011), CEP135 (EMBO J 2013), CEP120 (J Cell Biol 2013, Genes & Dev 2021), RTTN (Nat Commun 2017), and Myosin Va (Nat Cell Biol 2019). In this talk, I combine molecular and cellular, conditional CPAP cEV knock-in mouse model, and hiPSC-derived organoid approaches to elucidate how these organelles (centrioles or cilia) are constructed and how mutations in these genes lead to primary microcephaly, ciliary diseases, and tumorigenesis in humans.

2026 Biomedical Research Symposium of National Health Research Institutes
-Invited Speakers-

Session 1: Cancer Research

Dr. Shaw-Jenq Sean Tsai, National Chung Cheng University/National Cheng Kung University
Dr. Tien Hsu, China Medical University
Dr. Ming-Shyue Lee, National Taiwan University
Dr. Wen-Chun Hung, National Health Research Institutes

Session 2: Medical Engineering

Dr. Wen-Chuan Kuo, National Yang Ming Chiao Tung University
Dr. Er-Yuan Chuang, Taipei Medical University
Dr. Yan-Jye Shyong, National Cheng Kung University
Dr. Chii-Wann Lin, National Health Research Institutes

Session 3: Biomedical Science 1

Dr. Kuo-I Lin, Academia Sinica
Dr. Shao-Chun Wang, China Medical University
Dr. Jen-Huang Huang, National Tsing Hua University
Dr. Su Hao Lo, National Health Research Institutes

Session 4: Neuroscience

Dr. Kuo-Chen Wei, Chang Gung Medical Foundation
Dr. Jun-An Chen, Academia Sinica
Dr. Hsiang-Yu Yu, Taipei Veterans General Hospital
Dr. Feng-Shiun Shie, National Health Research Institutes

Session 5: Biomedical Science 2

Dr. Yu Feng Hu, National Yang Ming Chiao Tung University
Dr. Cheng-Chang Chen, National Taiwan University
Dr. Chun-Mei Hu, Academia Sinica
Dr. Chia-Yi Yu, National Health Research Institutes

Session 6: Clinical and Public Health

Dr. Ming-Tsang Wu, Kaohsiung Medical University
Dr. Chu-Lin Tsai, National Taiwan University
Dr. Ming Yen Lin, Kaohsiung Medical University
Dr. Chih-Cheng Hsu, National Health Research Institutes

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E-mail: seantsai@ccu.edu.tw

Education

1982-1986	B.S. National Cheng-Kung University, Taiwan
1990-1992	M.S. Eastern Michigan University, USA
1993-1997	Ph.D. University of Wisconsin-Madison, USA

Research and Professional Positions Held in Chronological Sequence

1998-2002	Assistant Professor, National Cheng Kung University, Taiwan
2002-2005	Associate Professor, National Cheng Kung University, Taiwan
2005-2008	Professor, National Cheng Kung University, Taiwan
2008-2019	Distinguished Professor, National Cheng Kung University, Taiwan
2019-2024	Chair Professor, National Cheng Kung University, Taiwan
2024-present	President and Chair Professor, National Chung Cheng University, Taiwan
2010-2011	Visiting Professor, Baylor College of Medicine, USA
2014-2017	Director General, Department of Life Sciences, Ministry of Science and Technology, R.O.C
2016-2020	President, The Chinese Physiological Society, Taiwan
2019-2020	President, Asian Society of Endometriosis and Adenomyosis
2012-present	Ambassador, World Endometriosis Society
2024-present	Editor-in-Chief, Journal of Physiological Investigation

Research Interests

My research interests focus on understanding the molecular mechanisms of human diseases. Our studies could be divided into two areas:

1. Endometriosis: Endometriosis is a common gynecological disease with the prevalence of 10-15 %. It is a complex disease with unknown etiology and severely reduces life quality of affected women and their family. We focus on local and epigenetic factors that cause inflammation in the peritoneal cavity, aberrant production of steroid hormones, angiogenesis, lymphangiogenesis, and suppression of immune function. Recent study extends to investigate systemic and microenvironmental factors contributing to endometriosis-associated infertility and to dissect their cellular and molecular mechanisms.

2. Cancer: Drug resistance is the most critical issue that contributes to treatment failure and mortality. Hypoxia is one of the most critical factors contributing to drug resistance. However, mechanisms responsible for hypoxia-mediated increased in drug resistance remain largely unknown. We have employed systems biology approach to investigate effects of hypoxia-

mediated gene regulatory networks in drug resistance and cancer malignancy. Current focuses are on the regulation of extracellular vesicles-mediated pancreatic cancer malignancy, functions of novel kinases in colon cancer metastasis and drug resistance, and loss-of-function of tumor suppressor gene in causing drug resistance and cancer malignancy.

Major Honors and Awards

2011	Distinguished Research Award, National Science Council
2014	Society for Experimental and Biology (SEBM) Distinguished Scientist Award
2018	Fellow, Society for Experimental Biology and Medicine
2018	Distinguished Research Award, Ministry of Science and Technology
2019	American Association for Cancer Research Most-Cited Article Award (Cancer Research 2017)
2020-2023	World's Top 2% Scientists
2021	Fuller W. Bazer SSR International Scientist Award, Society for the Study of Reproduction
2021	The Ministry of Education's 65th Annual Academic Awards
2022	International Union of Physiological Sciences Academy Fellow
2025	The 21st Tien Te Lee Outstanding Biomedical Award

Selected Publications

1. HT Hou, WN Li, TC Lin, CJ Lee, YJ Chen, YC Chen, PF Chen, CY Wang, MH Wu#, SJ Tsai# Disruption of primary ciliary prostaglandin E_2 signaling by transforming growth factor-β1 impairs endometrial receptivity. **J Biomed Sci** 33:28, 2026.
2. SC Lin#, YC Tsai, JL Wang, HJ Chin, CC Tsai, SC Lin, YS Lin, BW Lin, SJ Tsai#. Targeting NUDT21-mediated alternative polyadenylation of oncogenes ameliorates colorectal cancer malignancy and metastasis. **Br J Cancer** 2026, https://doi.org/10.1038/s41416-026-03451-9.
3. CA Wang, YC Hou, YJ Tai, YK Hong, PC Hou, JL Fu, CL Wu, SM Cheng, DY Hwang, YY Su, YS Shan#, SJ Tsai# Intercellular TIMP-1-CD63 signaling directs the evolution of immune escape and metastasis in KRAS-mutated pancreatic cancer cells. **Mol Cancer 24**, 25, 2025.
4. SC Lin, WN Li, SC Lin, HT Hou, YC Tsai, TC Lin, MH Wu#, SJ Tsai# Targeting YAP1 ameliorates progesterone resistance in endometriosis. **Hum Reprod** 38 (6): 1124-1134, 2023.
5. PL Hsu, CW Chien, YA Tang, BW Lin, SC Lin, YS Lin, SY Chen, HS Sun#, SJ Tsai# Targeting BRD3 eradicates nuclear TYRO3-induced colorectal cancer metastasis. **Sci Adv** 9(15): eade3422, 1 2023.
6. CB Chu, CC Yang, YY Hsueh, PC Chen, YK Hong, YY Kuo, S-J Tsai# Aberrant expression of IL-17A in mast cells contributes to the pathogenesis of hidradenitis suppurativa. **Br J Dermatol** 189(6):719-729, 2023.
7. WN Li, KY Hsiao, CA Wang, N Chang, PL Hsu, CH Sun, SR Wu, MH Wu#, SJ Tsai# Extracellular vesicle-associated VEGF-C promotes lymphangiogenesis and immune cells infiltration in endometriosis. **Proc Natl Acad Sci USA** 117 (41): 25859-25868, 2020.
8. CA Wang, YH Chang, PC Hou, YJ Tai, WN Li, PL Hsu, SR Wu, CF Li, YS Shan, SJ Tsai# DUSP2 regulates extracellular vesicle-VEGF-C secretion and pancreatic cancer early dissemination. **J Extracell Vesicles** 9 (1): 1746529, 2020
9. PS Chen, WT Chiu, PL Hsu, SC Lin, IC Peng, CY Wang, SJ Tsai# Pathophysiological implications of hypoxia in human diseases. **J Biomed Sci** 27: 63, 2020.

How Early *KRAS*-Mutated Pancreatic Cells Escape Oncogene-Induced Senescence and Immune Surveillance

Chu-An Wang[1, 2] and Shaw-Jeng Tsai[2, 3]
王竹安，蔡少正

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[2]Department of Physiology, National Cheng Kung University, Taiwan
[3]Department of Biomedical Sciences, National Chung Cheng University, Taiwan

Pancreatic cancer, the most notorious cancer, is a highly aggressive malignant tumor. Due to the lack of biomarkers for early diagnosis, it is often diagnosed at an advanced stage, making surgical resection impossible and resulting in poor response to chemotherapy, with a survival rate of less than 10%. Therefore, identifying the mechanisms of malignant transformation in pancreatic cancer is crucial. KRAS oncogene mutation is a key characteristic of pancreatic cancer, found in approximately 90% of pancreatic cancer samples. However, KRAS gene mutation alone is insufficient to cause pancreatic cancer. Our bodies have a protective mechanism that leads to the death of these abnormal cells. Using pancreatic samples from genetically modified mice and single-cell RNA-sequencing analysis of early and late-stage human pancreatic cancer samples, we discovered a small group of KRAS-mutated cells that increased with the progression of pancreatic cancer. Further analysis revealed that this group of cells lacked the expression of dual specificity phosphatase-2 (DUSP2). Through cell-chat analysis, we identified a specific group of macrophages in the tumor microenvironment that played a key role. When macrophages interact with pancreatic cancer cells, they inhibit the expression of DUSP2, thereby continuously activating extracellular signaling regulatory protein kinases and initiating mechanisms that promote tumor cell proliferation, metastasis, and immune evasion. Through pancreatic cancer RNA sequencing databases, we discovered a novel TIMP1-CD63 signaling pathway, a crucial mechanism for the mutual regulation between macrophages and cancer cells. Through this communication mechanism, cancer cells gain immune privilege, not only escaping elimination by the immune system but also rendering state-of-the-art cellular immunotherapy ineffective.

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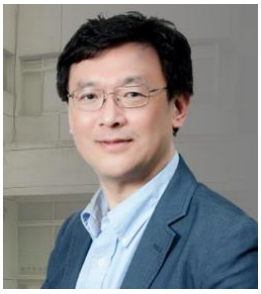

Education

1977-1981	Bachelor, Department of Agricultural Chemistry, National Taiwan University, Taiwan
1983-1988	Ph.D., Program in Molecular and Cell Biology and Pathobiology, Medical University of South Carolina, USA

Research and Professional Positions Held in Chronological Sequence

1989-1993	Postdoc, Department of Cellular and Developmental Biology, Harvard University, USA
1993-1997	Assistant Professor, Department of Experimental Oncology, Medical University of South Carolina, USA
1997-1999	Assistant Professor, Department of Cell Biology and Anatomy, Medical University of South Carolina, USA
1999-2003	Associate Professor, Department of Cell Biology and Anatomy, Medical University of South Carolina, USA
1999-2006	Associate Professor, Department of Pathology and Lab. Medicine, Medical University of South Carolina, USA
2006-2009	Professor, Department of Pathology and Lab. Medicine, Medical University of South Carolina, USA
2009-2013	Professor, Department of Medicine, Boston University School of Medicine, USA
2013-present	Professor, Institute of Systems Biology and Bioinformatics, National Central University, Taiwan
2014-present	Professor, Department of Biomedical Sciences and Engineering, National Central University, Taiwan Dean, College of Health Sciences and Technology, National Central University, Taiwan

Research Interests

Dr. Tien Hsu was recruited to the National Central University in August 2013. Previously he was Professor of Medicine at the Boston University School of Medicine. The major research interest in Dr. Hsu's laboratory is to understand the origin of cancer and the mechanism of its growth. In the 1990s, Dr. Hsu pioneered the study using multiple model organisms, including fruit fly, mouse, and human cells, for functional comparison of tumor-related genes in embryonic development. He has contributed greatly in the understanding of tumor suppressor genes VHL and anti-metastasis gene

Nm23. He serves on the advisory board of the International VHL Disease Alliance. He was elected in 2012 as the Chair of International Congress of NDPK/Nm23/awd Gene Family. He also served as grant review panel members of NIH (USA), and government agencies of other countries such as Italy, Israel, United Kingdom, Canada, Holland, etc.

Traditionally, cancer research has been focused on killing cancer cells. Such strategy has shown only limited success in the over 40 years of "War on Cancer". Dr. Hsu believes that we need to rethink our strategy, and should focus on the role of stromal cells, which promote inflammatory reaction and support stem cell survival. It is now discovered that tumor growth and stem cell maintenance are dependent on the surrounding tissues and cells (the stroma). Controlling organ pathology by modulating the stromal function should present a gentler and more effective containment of many diseases including cancer. The concept is to contain the cancer tissue and prevent malignancy, but not necessarily to kill cancer cells. Such new direction requires a systems biology view of the interaction between the diseased tissue and the entire body. Dr. Hsu's current research is focused on stromal biology, characterizing the function and therapeutic potential of the tumor microenvironment. He recently established that metabolic abnormality in VHL mutant cells can lead to ER stress and tissue inflammation, eventually resulting in clear-cell renal cell carcinoma formation.in clear-cell renal cell carcinoma,

More recently he initiated an integrated program project to analyze immune cell populations that mark the transition from inflammation to renal cell carcinoma at the single cell level.

Major Honors and Awards

1981	Fukian Association Scholarship
1983-1987	MUSC Graduate Fellowship
1987	-First Prize, Ph.D. Poster Section, MUSC Student Research Day -Grand Prize for Best Science, MUSC Student Research Day -Grand Prize for Best Presentation and Delivery, MUSC Student Research Day
1989	NIH Postdoctoral Research Fellowship
2007	Best Presentation, 7th International Congress of the NDP Kinase/NM23/awd Family, Dundee, UK
2008-present	Member, International VHL Alliance Research Council
2012-2013	President of International Congress of the NDP Kinase/NM23/awd Gene Family
2012-2017	Led an NCU team that won the second prize (total 255 teams) in International Qualcomm Tricorder XPrize
2013	Distinguished Researcher, NCU
2014-present	-University Chair Professor in Biomedicine, NCU -Taiwan Bio-development Foundation (TBF) Chair in Biotechnology

How Do Cancer Cells Get Their Fats?

Thi-Ngoc Nguyen,[1,5] Hieu-Huy Nguyen-Tran,[1,5] Kuo-How Huang,[2] Kuan-Lin Kuo,[2,3] Shih-Ming Liao,[2] Wei-Chou Lin,[4] and Tien Hsu[1*]

[1]Graduate Institute of Biomedical Sciences, China Medical University, Taiwan,
[2]Department of Urology, College of Medicine, National Taiwan University, Taiwan,
[3]Graduate Institute of Toxicology, College of Medicine, National Taiwan University, Taiwan,
[4]Department of Pathology, College of Medicine, National Taiwan University, Taiwan,
[5]These authors contributed equally

Clear-cell renal cell carcinoma (ccRCC) is defined by cancer cells with lipid-filled cytoplasm that appears "clear" in tissue preparations**;** however, the origin of these lipids and their role in tumor progression remain unclear. Notably, cultured ccRCC cells rarely exhibit the clear-cell phenotype *in vitro*, suggesting that lipid accumulation in ccRCC is not cell-autonomous. Here we show that tumor-associated macrophages (TAMs) undergo immunometabolic reprogramming and serve as major suppliers of lipids for ccRCC cells. Upon activation by the tumor suppressor gene *VHL*-deficient kidney tubule cells, TAMs acquire adipogenic and cholesterol metabolic signatures, accumulate lipids, and differentiated into lipid-laden macrophages (LLMs) via a TGF-β-APOE-dependent pathway. LLMs then transfer lipids directly to tumor cells through tunneling nanotubes (TNTs). Lipidomic analyses revealed that LLMs and recipient tumor cells share nearly identical lipid profiles enriched in cholesterol and phosphatidates, but not triglycerides. In patient cohorts, elevated APOE expression levels in macrophages (MΦs) correlated with advanced disease stages. *In vivo*, disruption of MΦ-specific APOE expression abrogated the clear-cell phenotype, reduced tumor growth, and suppressed metastasis in autochthonous and orthotopic xenograft ccRCC models. These findings identify a previously unrecognized MΦ-tumor crosstalk in which reprogrammed TAMs supply lipids to tumor cells, driving the clear-cell phenotype and disease progression. Targeting the TGF-β-APOE axis or TNT-mediated lipid transfer represents a potential therapeutic strategy. More broadly, this work supports a "metabolic checkpoint" paradigm, revealing a therapeutically amenable vulnerability in ccRCC.

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Education

1992	B.S., Department Of Agricultural Chemistry, National Taiwan University Taiwan
1994	M.S., Institute of Biological Chemistry, National Taiwan University, Taiwan
2002	Ph.D., Department Of Biochemistry and Molecular Biology, University Of Nebraska Medical Center, Omaha, NE

Research and Professional Positions Held in Chronological Sequence

2003	Post-Doctoral Research Associate, Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE
2003-2006	Postdoctoral Fellow, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, District of Columbia.

Research Interests

Our research focuses on three integrated objectives: (1) elucidating the molecular mechanisms underlying prostate cancer progression and metastasis; (2) identifying robust biomarkers to distinguish clinically significant (lethal) from indolent prostate cancer; and (3) defining the mechanisms of action of targeted therapies and their impact on tumor-immune interactions.

We investigate the role of cell surface proteolysis in cancer biology, particularly the Type II transmembrane serine proteases (TTSPs), which regulate key processes such as extracellular matrix remodeling, cell proliferation, migration, and apoptosis. Dysregulation of TTSPs contributes to tumor growth, invasion, and metastasis. Our work specifically examines TMPRSS2, matriptase, and matriptase-2, along with their cognate inhibitors HAI-1 and HAI-2, in prostate and lung cancer progression. In parallel, we study the pathological roles of HAI-1 and HAI-2 in biliary atresia and cholangiopathies, as well as the physiological function of the HAI-1-hepsin axis in pancreatic β-cell insulin production.

To address the clinical limitations of prostate-specific antigen (PSA)-based screening, including false positives, overdiagnosis, and overtreatment, we are developing noninvasive urinary biomarkers to improve early detection and risk stratification, enabling more precise treatment decision-making.

In addition, our recent findings reveal an unexpected immunomodulatory role for the EGFR tyrosine kinase inhibitor afatinib. Sequential administration of afatinib prior to anti-PD-1 therapy enhances antitumor efficacy, promotes $CD8^+$ T-cell infiltration, and prolongs survival in preclinical models. Building on this, we aim to define how afatinib functions not only as a tumor-intrinsic EGFR inhibitor but also as a transient immune-modulating agent that augments adaptive antitumor immunity.

Decoding Lethal Prostate Cancer: Urinary Biomarkers and the Functional Role of Pericellular Serine Proteases

Ming-Shyue Lee
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Department of Biochemistry and Molecular Biology, National Taiwan University, Taiwan

Prostate cancer exhibits substantial clinical heterogeneity, ranging from indolent disease to rapidly progressive and lethal forms. The inability to reliably distinguish aggressive tumors from clinically insignificant cases remains a critical challenge, often leading to overdiagnosis and overtreatment. To address this unmet need, our research integrates the development of non-invasive urinary biomarkers with mechanistic studies of molecular drivers underlying prostate cancer progression.

Using untargeted mass spectrometry-based metabolomics and proteomics, we have identified and validated panels of urinary metabolites and proteins that effectively stratify lethal or clinically significant prostate cancer from indolent disease. Notably, the integration of urinary metabolite biomarkers with clinical parameters achieved an area under the curve (AUC) of approximately 0.9 for predicting both prostate cancer and lethal disease. Similarly, protein biomarker panels combined with clinical factors demonstrated comparable predictive performance, with AUCs approaching 0.90. These findings highlight the potential of urine-based molecular profiling as a robust, non-invasive approach that improves diagnostic accuracy beyond conventional methods.

To further elucidate the biological basis of lethal prostate cancer, we investigate the functional roles of pericellular serine proteases, including matriptase, matriptase-2, and TMPRSS2, along with their cognate inhibitors. Mechanistic analyses revealed that dysregulated protease activity drives prostate cancer progression by promoting tumor cell invasion, enhancing tumor growth, and facilitating metastatic dissemination. Imbalance within protease-inhibitor network contributes to extracellular matrix remodeling and activation of downstream signaling pathways that collectively support tumor aggressiveness.

Collectively, our work advances the understanding of prostate cancer biology by non-invasive biomarker discovery and mechanistic insights into protease-driven tumor progression. This integrated approach provides a promising framework for improved risk stratification and identifies potential therapeutic targets for the management of lethal prostate cancer.

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Education

1981-1985	BS, School of Technology for Medical Science, Kaohsiung Medical University
1985-1987	Master, Institute of Neuroscience, Yang-Ming Medical University
1990-1994	PhD, Institute of Medicine, Kaohsiung Medical University

Research and Professional Positions Held in Chronological Sequence

1999-2004	Professor, School of Technology for Medical Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan
2000-2001	Chair, Division of Registration and Curriculum, Office of Academic Affairs, Kaohsiung Medical University, Kaohsiung, Taiwan
2004-2008	Director and Distinguished Professor, Institute of Biomedical Sciences, National Sun Yat-Sen University
2008-2011	Dean and Xi-Wan Chair Professor, College of Science, National Sun Yat-Sen University
2010-2011	Chair, Domain of Microbiology, Immunology and Medical Technology, National Science Council, Taiwan, Republic of China
2011/06-2018/10	Deputy Director, National Institute of Cancer Research, National Health Research Institutes
2018/12-2021/07	Vice President and Distinguished Professor, Kaohsiung Medical University
2021/08-2022/08	Director, Research Planning and Development, National Health Research Institutes
2022/01~	Distinguished Investigator, National Institute of Cancer Research, National Health Research Institutes
2023/02~	Secretary General, National Health Research Institutes
2023/09-2024/07	Acting Director, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes
2023/05~	Boards of Director, The Chinese Society of Cell and Molecular Biology

Research Interests

Cancer Biology, Pancreatic Cancer GEM model, Lymphangiogenesis and Tumor Metastasis, Anti-Cancer Drug Development

Major Honors and Awards

2003	The Outstanding Research Award, National Science Council, ROC
2004	Dr. Chien-Tien Hsu's Outstanding Cancer Research Award, The Chinese Oncology Society, ROC
2004-2008	Distinguished Research Professor, National Sun Yat-Sen University, Taiwan, ROC
2005	The 1st Yung Shin Lee Tian-De Medical and Pharmaceutical Science and Technology Awards-Young Scientist Research Scholarship, ROC
2009-2011	Xi-Wan Chair Professor, National Sun Yat-Sen University, Taiwan, ROC
2010-2011	Chair, Domain of Microbiology, Immunology and Medical Technology, National Science Council, Taiwan, ROC
2020	Outstanding Research Award for Memory Lecture of Pin-Wen Lin, The 13th International Pancreatic Cancer Conference, ROC
2021-2024	World's Top 2% Scientists, Stanford University, USA
2022	Distinguished Investigator, National Institute of Cancer Research, National Health Research Institutes, ROC
2024	Dr. Tung Ta-Cheng's Basic Cancer Research Award, Taiwan Oncology Society, ROC
2024	The 21st National Innovation Award: University-Institute Innovation Award, Taiwan, ROC

Representative Works (2023~) (*corresponding author)

1. TL Kuo, KH Cheng, LT Chen, **WC Hung***. (2023, Jan) ARID1A loss in pancreas leads to islet developmental defect and metabolic disturbance. ***iScience.*** 26(1):105881. (IF=5.8, MULTIDISCIPLINARY SCIENCES, RANK=15/73, Q1)
2. Hsu SH, **Hung WC***. (2023, Feb) Protein arginine methyltransferase 3: A crucial regulator in metabolic reprogramming and gene expression in cancers. ***Cancer Letters.*** 554:216008. (IF=9.7, ONCOLOGY, RANK=34/241, Q1)
3. SH Hsu, YL Tsai, YT Wang, CH Shen, YH Hung, LT Chen, **WC Hung***. (2024, Mar) RNF43 Inactivation Enhances the B-RAF/MEK Signaling and Creates a Combinatory Therapeutic Target in Cancer Cells. ***Advanced Science.*** 11(12):e2304820. (IF=15.1, CHEMISTRY, MULTIDISCIPLINARY, RANK=16/178, Q1)
4. Kuo TL, Hou YC, Shan YS, Chen LT, **Hung WC***. (2025, Jul) ARID1A deficiency sensitises pancreatic cancer to fatty acid synthase inhibition. ***Clin Transl Med***. 15(7):e70394.
5. CT Liu, YY Su, NJ Chiang, CF Li, YC Ma, KC Chang, YH Hung, **WC Hung***, LT Chen*. (2026, Feb) Mutant Isocitrate dehydrogenase 1 sensitizes intrahepatic cholangiocarcinoma cells to MDM2 inhibitors. ***Cancer Res Commun***. doi: 10.1158/2767-9764.CRC-25-0591. Online ahead of print.

Vulnerable Therapeutic Targets in ARID1A-deficient Pancreatic Cancer

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The mutations in the SWI/SNF chromatin remodeling complex occur in nearly 25% of all human cancers and the ARID1A gene is the most frequently mutated component in the complex. ARID1A is dysregulated in many pancreatic cancer patients. However, its function in pancreas development, endocrine regulation and tumorigenesis remains largely uncharacterized. We generated a genetically engineered mouse model harboring both K-ras mutation and ARID1A depletion (KAR mice) and showed that the combination of these two genetic alterations induces pancreatic tumor formation. Compared to the tumors developed in mice with K-ras mutation and Tp53 deficiency (KPC mice), KAR tumors exhibited a significant increase in fatty acid synthase (FASN) expression and lipid metabolism. Inhibition of FASN by chemical inhibitor reduced ARID1A -deficient tumor cell viability and slowed tumor progression in mice. Metabolomics analysis revealed a unique lipid reprogramming program in ARID1A-deficient pancreatic cancer cells and sensitized the cells to ferroptosis induction. Moreover, neutrophil infiltration was significantly increased in the KAR tumors which induces an immunosuppressive microenvironment. We developed a humanized anti-CXCR2 antibody and showed its potency in inhibiting neutrophil infiltration and growth of the KAR tumors. Collectively, we identify several vulnerable therapeutic targets in ARID1A-deficient pancreatic cancer which could be translated into future clinical application.

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Education

1995-1999	B.S., Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taiwan
1999-2001	M.S., Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taiwan
2001-2005	Ph.D., Electrical Engineering, National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2005-2009	Assistant Professor, Institute of Electro-optical Science and Technology, National Taiwan Normal University
2009-2011	Associate Professor, Institute of Electro-optical Science and Technology, National Taiwan Normal University
2011-2015	Associate Professor, Institute of Biophotonics, National Yang-Ming University
2015-Present	Professor, Institute of Biophotonics, National Yang-Ming University
2015-Present	Joint Appointment Professor, Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University
2016-2017	Medical Equipment Consultant, Taiwan Food and Drug Administration (TFDA), Taiwan
2016-2018	Chairman, Institutional Animal Care and Use Committee (IACUC), NYMU
2019-2023	Distinguished Professor, Institute of Biophotonics, National Yang-Ming University
2020-2026	Director, Institute of Biophotonics, National Yang Ming Chiao Tung University
2020-2026	Director, Bachelor program of Digital Healthcare, NYCU
2020-Present	Permanently Exempt Assessment Teacher, NYMU
2021-2022	Associate Dean of Research & Development Affairs, NYCU

Research Interests

Biomedical optics and biophotonics; optical coherence tomography (including polarization-sensitive and angiographic OCT); handheld and probe-based optical imaging systems; machine learning and deep learning for biomedical imaging; translational imaging applications in cancer detection, ophthalmology, and image-guided procedures.

Major Honors and Awards

2009-2011	Academic Research Excellent Teacher, National Taiwan Normal University
2000-2001	Special Talents Incentive Award, National Taiwan Normal University
2011-2017	Academic Excellence Award, National Yang-Ming University
2015-2016	Teaching Evaluation Excellent Teacher, National Yang-Ming University
2016	Excellent Teaching Award, National Yang-Ming University
2019-2021	Academic Excellence Award, National Yang-Ming University
2020	FutureTech Award, Taiwan
2020	Permanently exempt assessment teachers, NYMU.
2022	National Innovation Award, Taiwan Bio Industry Organization
2023	Outstanding Team Award, NBRP Pitch Day
2024	Chang Ming-Wen Young Optical Science and Technology Award, Optical Engineering Society of the Republic of China

Translational Development of a Handheld Multiparametric PS-OCTA System for *In Vivo* 5D Optical Biopsy and Early Oral Oncology

Wen-Chuan Kuo
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Institute of Biophotonics, National Yang Ming Chiao Tung University, Taiwan

Oral squamous cell carcinoma (OSCC) survival rates remain stagnant due to delayed diagnosis and subjective screening methods. This translational study introduces a handheld, multiparametric polarization-sensitive optical coherence tomography angiography (PS-OCTA) system for *in vivo* "5D optical biopsy". Initial research using mouse models established that quantitative biomarkers—including IPCL density, radius, and tortuosity—increase sequentially during carcinogenesis, while en-face birefringence maps achieved 100% sensitivity in detecting early-stage malignancy. These laboratory findings were translated into a clinical-grade 100 kHz handheld probe equipped with a disposable hygiene sleeve and refined algorithms to eliminate polarization-induced artifacts. The system extracts five dimensions of tissue data—differential intensity, phase retardation, DOPU, fast axis orientation, and 3D vasculature—allowing for an objective assessment of tissue stratification and collagen integrity within seconds. Human clinical testing successfully mapped various mucosal structures. By providing high-resolution, non-invasive alternatives to traditional biopsies, this technology offers a powerful framework for early cancer screening and precise tumor margin definition in a clinical setting.

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Education

2003-2007	B.S. in Department of Chemical Engineering, TamKang University, Taipei, Taiwan
2007-2009	M.S. in Institute of Biomedical Engineering, National Taiwan University, Taiwan
2009-2013	Ph. D. in Institute of Biomedical Engineering, National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2016–2020	Assistant Professor, Graduate Institute of Biomedical Materials and Tissue Engineering, Taipei Medical University, Taiwan
2018–Present	Board Member, Taiwan Chitin and Chitosan Society, Taiwan
2020–2023	Associate Professor, Graduate Institute of Biomedical Materials and Tissue Engineering, Taipei Medical University, Taiwan
2021–Present	Founder, Hsuan-Chen Biomedical Technology Co., Ltd., a Taipei Medical University spin-off company, Taiwan
2023–2024	Professor, Graduate Institute of Biomedical Materials and Tissue Engineering, Taipei Medical University, Taiwan
2024–Present	Professor and Director, Graduate Institute of Biomedical Materials and Tissue Engineering, Taipei Medical University, Taiwan

Research Interests

- Smart Biomimetic Medical Materials

Our work focuses on smart biomimetic medical materials inspired by cells, photosynthetic microorganisms, and naturally derived vesicles. These systems provide active functions such as oxygen generation, immune modulation, microenvironmental regulation, and stimulus-triggered therapy, moving beyond conventional passive biomaterials.

- Polysaccharide-Based Polymers and Composite Medical Materials

We are developing polysaccharide-based and composite medical materials, including chitosan, glycol chitosan, alginate, fucoidan, carrageenan, and hyaluronic acid systems. These materials have been applied to hydrogels, nanocarriers, wound dressings, scaffolds, and regenerative platforms for wound healing, cartilage repair, cancer therapy, and inflammatory disease treatment.

- Physically, Biochemically, and Environmentally Driven Biomaterial Technologies

Our research emphasizes biomaterials activated by physical, biochemical, or environmental cues, such as light, heat, magnetic fields, plasma treatment, redox reactions, enzymes, and pathological signals. These systems can generate photothermal, photoelectric, oxygen-releasing, immunomodulatory, antibacterial, and tissue-repairing effects.

- Clinical Translational Applications of Nanomedicine Delivery Systems and Tissue Engineering

A central goal of my research is to bridge biomaterials science with clinical translation. Our platforms have been explored in cancer, thrombosis, diabetic wounds, osteoarthritis, rheumatoid arthritis, bladder disorders, ophthalmic diseases, and regenerative medicine to develop safer and more effective therapeutic strategies.

- Applications of Plasma and Liquid Crystal Technologies in Precision Biomedical Engineering

We have explored plasma and liquid crystal technologies for precision biomedical engineering. Plasma technology improves the surface chemistry and biological performance of polymeric biomaterials, while liquid crystal systems provide rapid, low-cost, and sensitive biomedical detection platforms.

Major Honors and Awards

- Taipei Medical University Outstanding Research Paper Award, 2025 (Academic Year 114)
- Taipei Medical University Annual Research Achievement Award, 2025 (Academic Year 114)
- National Innovation Award - Innovation Advancement Award (2021-2025)
- Wanfang Hospital Excellent Paper Award (2021-2025)
- Taipei Medical University Hospital High Point Index Award for Outstanding Papers (2023-2025)
- Journal of Nanobiotechnology | Outstanding Reviewer Award (2024-2025)
- 2025 National Science Council 114th Annual "2030 Transgenerational Young Scholars Program | Outstanding Young Scholars Research Project"
- Sigma Xi The Scientific Research Honor Society (2025)
- The 7th Taiwan International Symposium on Regenerative Medicine Materials and the Annual Meeting of the Chinese Society for Biomedical Materials and Drug Manufacturing - Invited Speakers
- National Science Council Research Grants for Colleges and Universities, 2012-2014 (Measures to Reward Exceptionally Outstanding Talents)
- Taipei Medical University Distinguished Research Paper Award, Academic Year 113 (2024)
- Taipei Medical University Distinguished Research Paper Award, Academic Year 112 (2023)
- Taipei Medical University Annual Research Achievement Award, Academic Year 112 (2023)
- 2023 Taipei United University System Academic Research Achievements Presentation (Oral Presentation Award of Excellence)
- Invited Speaker, Taiwan Society of Chemical Engineers (2022)
- Annual Meeting of the Chinese Society for Biomedical Materials and Drug Manufacturing & Presentation of Achievements in Engineering Medicine, Department of Life Sciences, National Science Council - Invited Speakers
- 110th Academic Year Taipei Medical University Young Scholar Research Award
- 110th Academic Year Taipei Medical University Outstanding Research Paper Award
- 2021 Ministry of Science and Technology Research Awards (Measures for Attracting and Rewarding Exceptionally Outstanding Talents)
- The 17th National Innovation Award - Academic and Research Innovation Award (2020)
- VEBLEO SCIENTIST AWARD (2020)

Cold Atmospheric Plasma-Reinforced Micro/Nano-Biomimicked Hybrid Carrier Loaded with Platelet Lysate for Enhanced Osteoarthritis Attenuation

Andrew E.-Y. Chuang
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Institute of Biomedical Engineering, National Taiwan University, Taiwan

Osteoarthritis (OA) is a prevalent chronic joint disorder in aging populations and is characterized by progressive cartilage degeneration, inflammation, oxidative stress, extracellular matrix degradation, and immune imbalance. Current therapeutic strategies, including analgesics, hyaluronic acid injection, platelet-rich plasma, biologics, and rehabilitation, primarily provide symptomatic relief but remain limited in prolonging therapeutic retention and actively regulating the OA microenvironment. In this study, we developed a platelet lysate (PL)-based nanocarrier hydrogel system to extend the therapeutic window and enhance the tissue-repair potential of PL for OA treatment. Glycol chitosan (GCS) and hyaluronic acid (HA) were employed as dual-polymer nanocarriers to encapsulate PL, and the resulting system was further incorporated into a Pluronic F127 thermosensitive hydrogel to improve intra-articular retention and sustained release. Cold atmospheric plasma (CAP) treatment was additionally applied to enhance material stability and local retention within the inflamed joint microenvironment. Mild and moderate OA animal models were established using anterior cruciate ligament transection (ACLT), followed by histological evaluation, OARSI scoring, fluorescence tracking, and biomarker analysis. The results showed that the PL-loaded nanocarrier hydrogel prolonged intra-articular retention, reduced IL-6, ROS, and CD44 expression, and promoted macrophage polarization from the M1 inflammatory phenotype toward the M2 reparative phenotype. Improved cartilage architecture, extracellular matrix preservation, and cartilage thickness were also observed, particularly in the moderate OA model. Safety evaluation revealed no obvious systemic toxicity. Overall, the PL/GCS/HA nanocarrier integrated with Pluronic F127 hydrogel and CAP treatment provides a multifunctional OA therapeutic platform with prolonged retention, immunomodulatory, anti-inflammatory, and antioxidant effects, supporting its potential for future translational development.

Keywords: Osteoarthritis; Platelet lysate; Nanocarrier hydrogel; Cold atmospheric plasma; Macrophage polarization

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Education

2002-2006	B.S., Biomedical Engineering and Environmental Sciences, National Tsing Hua University
2009-2011	M.S., Biomedical Engineering, National Yang-Ming University
2011-2017	Ph.D., Biomedical Engineering, National Taiwan University

Research and Professional Positions Held in Chronological Sequence

2016-2017	National Institute for Materials Science (NIMS), Nanotechnology Innovation Station, Japan
2017-2019	University of California San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, USA
2019-2024	Assistant Professor, School of Pharmacy, National Cheng Kung University, Taiwan
2020-2023	Jointly Appointed Assistant Professor, Biomedical Engineering, National Cheng Kung University, Taiwan
2024-present	Associate professor, School of Pharmacy, National Cheng Kung University, Taiwan

Research Interests

Drug delivery system, Biomaterials, Cell therapy, Cancer immunotherapy, Gene delivery

Major Honors and Awards

2019	Annual Meeting of the Biomaterials and Controlled Release Society (BCRS), Outstanding Young Investigator Award
2023	International Symposium on Materials for Regenerative Medicine (ISOMRM), Young Investigator Award
2024	Global Conference on Biomedical Engineering (GCBME), Outstanding Paper Award
2024	Taiwan Pharmacy Joint Academic Conference, Best Paper Award
2025	Cheng-Hsing Medical Foundation, Outstanding Research Paper Award

3D-Printed Intervertebral Cages for rhTMD2/3 Delivery to Enhanced Implant Stability and Spinal Fusion

Cheng-Li Lin[1], Wei Huang[2], Cheng-Hsiang Kuo[3], Yuan-Fu Liu[1], Jui-Chen Tsai[4], Ting-Yuan Tu[2] and Yan-Jye Shyong[4]*
林政立[1], 黃偉[2], 郭承翔[3], 劉元甫[1], 蔡瑞真[4], 涂庭源[2], 熊彥傑[4]*

1 Department of Orthopedic Surgery, National Cheng Kung University, Taiwan
2 Department of Biomedical Engineering, National Cheng Kung University, Taiwan
3 Department of Physiology, National Cheng Kung University, Taiwan
4 School of Pharmacy, College of Medicine, National Cheng Kung University, Taiwan

Spinal interbody fusion is frequently complicated by mechanical instability, cage subsidence, and biological failure (pseudoarthrosis). Current clinical standards rely heavily on non-degradable polyetheretherketone (PEEK) and titanium cages, which lack anatomical conformity and actively hinder natural bone healing. To overcome these limitations, this study presents a comprehensive dual-component biomaterial system designed to seamlessly bridge early-stage mechanical stabilization and long-term osteointegration.

The primary structural component is a customized 3D-printed polyethylene glycol diacrylate (PEGDA) fusion cage, tailored to the patient's specific intervertebral disc space using preoperative CT imaging to minimize subsidence risk. The cage features barbed surface macro-structures to drastically increase interfacial friction for immediate postoperative stability, alongside an internal porous mesh architecture to facilitate cellular infiltration. Crucially, simvastatin (SIM) is uniformly incorporated into the matrix during non-thermal stereolithography (SLA) 3D printing, thereby protecting the drug from thermal degradation. The sustained local release of SIM actively stimulates osteogenesis, directing newly forming bone cells from the vertebral endplates deep into the porous mesh to securely anchor the implant.

To biologically complement the mechanical support of the cage, we formulated a biodegradable calcium phosphate (CAP) micro-particle graft designed to deliver recombinant human thrombomodulin (rhTMD2/3). Unlike inert clinical cements, the CAP micro-carrier mimics natural bone minerals and degrades safely over time. RhTMD2/3 is a highly potent therapeutic protein containing six EGF-like domains that robustly induce local cell proliferation and migration. Encapsulating rhTM within the slow-degrading CAP carrier ensures a controlled, sustained release profile that maximizes tissue regeneration while strictly preventing local toxicity.

This synergistic system was evaluated using an *in vivo* rat caudal disc interbody fusion model. By pairing the structurally supportive SIM-loaded cage with the biologically active CAP-rhTM graft, we created an optimized regenerative microenvironment. This dual-drug, bio-instructive approach offers an innovative, fully biodegradable, and highly effective alternative to current clinical standards for spinal fusion surgery.

Keywords: 3D printed fusion cage; Simvastatin; Calcium phosphate micro-particles; Recombinant human thrombomodulin (rhTMD2/3); Interbody fusion; Implant stability.

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Education

1980-1984	B.S, Electrical Eng, National Cheng-Kung University, Taiwan.
1984-1986	M.S, Biomedical Eng, National Yang-Ming University, Taiwan.
1988-1993	Ph.D, Biomedical Eng, Case Western Reserve University, USA.

Research and Professional Positions Held in Chronological Sequence

1990 - 1992	Graduate Research Assistant – Otto Sensors Inc.
1993 - 1993	Research Associate – Neurology Dept., CWRU
1993 - 1995	Assist. Research Fellow – Dept. Biomed Eng., NTUH
1995 - 2006	Adj. Assoc. Prof. – Inst. BME, National Yang-Ming Univ.
1996 - 2002	Adj. Assoc. Res. – Fellow Dept. Biomed Eng., NTUH
1988 - 1998	Visiting Assoc. Prof. – CWRU Edison Design Center
1995 - 1998	Assoc. Research Fellow – BME Res. Center, Med. School, NTU
2002 - 2006	Assoc. Prof. – Elect. Eng. Dept., NTU.
1998 - 2006	Assoc. Prof. – Dept. Biomed. Eng. NTU.
2023 - Present	Joint Professors – Biotech Research Center, NTU.
2022 - Present	Joint Professors – Grad. School of Advanced Tech., NTU.
2007 - Present	Joint Professors – Inst. Applied Mech., NTU.
2006 - Present	Joint Professors – Inst. Bioelect. & Bioinform., NTU.
2006 - Present	Full Professor – Dept. Biomed. Eng. NTU
2017 - 2023	Director General & V.P. – BDL, ITRI
2007 - Present	Senior Research Fellow – BDL, ITRI
2023 - Present	Visiting Professor – Center for Artificial Intelligence Research, University of Tsukuba.
2024 - Present	Specialist – Sci. & Tech. Policy Advisory Office, NSTC
2025 - Present	Distinguished Investigator & Director – Inst. Biomed Eng. & Nanomedicine., NHRI.

Research Interests

Neural Engineering, Medical Microsensor & System, Medical Optics, Regulatory Affairs.

Professional Societies

- IEEE EMBS, LEOS, SMCS Members
- Taiwan BMES, Permanent Member

- Taiwan Chemical Sensor Association, Permanent Member, Auditor, Former President
- Taiwan MEMS Society, Permanent Member, Auditor

Major Honors and Awards

2020	RD100 Awards - iKNOBEADS
2021	RD100 Awards - 3D printed BioMS-Ti
2022	Edison Awards Silver Prize – 3D printed BioMS-Ti
2023	Edison Awards Bronze Prize – iRFA Devices & System
2025	Edison Awards Gold – Dual-Phase Hydrogel

Advanced Sensing Technologies and Progress in Organoid Applications

Chii-Wann Lin
林啟萬

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

The FDA Modernization Act 3.0 (MA 3.0) and its associated Innovative Science and Technology Approaches for New Drugs (ISTAND) program have catalyzed a paradigm shift in preclinical development by endorsing human-relevant, non-animal testing models, such as Artificial Intelligence, Microphysiological systems, organ-on-a-chip and organoid platforms, for safety and efficacy assessments. In alignment with this regulatory initiative, significant progress has been made in the development and application of 3D salivary gland organoids cultured within automated microfluidic systems. These dynamic culture environments elevate acinar differentiation rates and enable continuous physiological monitoring, overcoming the limitations of traditional, manual endpoint assays. To comprehensively evaluate these organoids without invasive procedures, a multimodal analytical platform has been developed, integrating several cutting-edge sensing technologies, including Advanced Surface Plasmon Resonance (SPR)[1], [2], Polarization-Resolved Microscopy[3], [4], Electrochemical and Dielectric Sensing[5], [6]. Collectively, the integration of these highly sensitive, non-invasive sensing technologies with microfluidic organoid models establishes a robust framework that fulfills the FDA MA 3.0 mandate. This multimodal approach provides continuous, reliable, and high-throughput data on morphological, mechanical, and biomolecular responses, paving the way for next-generation precision medicine.

1. T.-H. WU et al., “Compact Shearing Interferometry Surface Plasmon Resonance biosensor based on VCSEL wavelength modulation,” Meas. Sci. Technol., Jan. 2026, doi: 10.1088/1361-6501/ae3e0d.
2. K.-J. Lin et al., “A machine learning-driven dip-searching algorithm for angle-resolved Surface Plasmon Resonance (aSPR) biosensing,” Sens. Actuators A Phys., vol. 395, p. 117104, Dec. 2025, doi: 10.1016/J.SNA.2025.117104.
3. J.-H. Yang et al., “Polarization-Resolved Microscopy for Label-Free Stress-Induced Birefringence Mapping in Anisotropic Organoids,” Jan. 2026. [Online]. Available: http://SPIE.org/manuscripts
4. C.-L. Chiang, N.-F. Chiu, J.-H. Yang, D.-J. Chang, and C.-W. Lin, “Layer-by-layer characterizations of protein complexes by surface plasmon resonance enhanced Raman system - detection of heparin-platelet factor IV complexes as an example,” Sens. Actuators B Chem., vol. 452, p. 139461, Apr. 2026, doi: 10.1016/J.SNB.2026.139461.
5. C. W. Lin et al., “Design and characterization of an LC-based resonator complementary metal-oxide-semiconductor circuitry for noncontact complex dielectric constant sensor system,” Bull. Chem. Soc. Jpn., vol. 98, no. 7, Jul. 2025, doi: 10.1093/BULCSJ/UOAF064.
6. X.-X. Lin, S.-H. Huang, C.-W. Lin, and Y. Peng, “An LC-Oscillator-based permittivity biosensor for microbial concentration measurement in milk for food safety,” 2024.

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Education

1987-1991	B.S., Medical Technology, National Taiwan University, Taiwan
1991-1993	M.S., Medical Technology, National Taiwan University, Taiwan
1993-1998	Ph.D., Molecular Microbiology and Immunology, The Johns Hopkins University, USA

Research and Professional Positions Held in Chronological Sequence

1998-2003	Post-doctoral Fellow, Microbiology and Immunology, Columbia University, USA
2003-2004	Associate Research Scientist, Microbiology and Immunology, Columbia University, USA
2004-2009	Assistant Research Fellow, Genomics Research Center, Academia Sinica, Taiwan
2009-2014	Associate Research Fellow, Genomics Research Center, Academia Sinica, Taiwan
2014-2022	Research Fellow, Genomics Research Center, Academia Sinica, Taiwan
2022-present	Distinguished Research Fellow, Genomics Research Center, Academia Sinica, Taiwan
2014-present	Division Director of Medical Biology, Genomics Research Center, Academia Sinica, Taiwan
2010-2016	Adjunct Associate Professor, Graduate Institute of Immunology, National Taiwan University, Taiwan
2016-present	Adjunct Professor, Graduate Institute of Immunology, National Taiwan University, Taiwan

Research Interests

1. Immunology
2. Glycoimmunobiology
3. B cell biology

Major Honors and Awards

1999	Phi Beta Kappa, The Johns Hopkins University, USA
1999-2002	The Leukemia and Lymphoma Society Fellowship, USA
2005	Li Foundation Heritage Prize
2008	1st ASAIHL-Scopus Young Scientist Award (Winner of Life Science)
2014	-Outstanding Research Award, National Science Council (MOST), Taiwan

	-Young Scientist Research Award, Tien-Te Lee Biomedical Foundation, Taiwan
	-Outstanding Research Award, The Chinese Society of Immunology, Taiwan
2015	Chair in Biotechnology, Taiwan Bio-Development Foundation
2017	Outstanding Research Award, Ministry of Science and Technology, Taiwan
2019	Outstanding Research Achievement to National Health, Ming-Ning Wang Memorial Foundation
2024	Chiung-Lin Chen Memorial Award for Translational Medicine, Taiwan

Mechanisms underlying B Cell Differentiation and Antibody-Mediated Protection

Kuo-I Lin
林國儀

Genomics Research Center, Academia Sinica, Taiwan

B cells are a unique type of immune cell that produce antibodies upon activation and differentiation. They provide long-term immunological memory and humoral immunity, which form the basis for successful vaccination. In addition to generating antibody-mediated immunity and serving as antigen-presenting cells, a distinct subset known as regulatory B cells (Bregs) can negatively regulate immune responses. Dr. Lin's laboratory studies the molecular mechanisms controlling B cell activation and differentiation. In this talk, she will discuss the mechanisms regulating B cell activation, plasma cell generation, and plasma cell maintenance, focusing specifically on transcriptional and post-translational regulation.

Antibodies play a key role in pathogen clearance. Dr. Lin's group employed a single B cell screening platform to isolate pathogen-specific antibodies, including those targeting influenza viruses and SARS-CoV-2. The mode of action of these monoclonal antibodies in combating viral infections will also be discussed.

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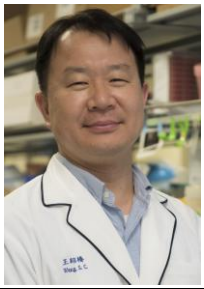

Education

1984-1988	B.Sc. - Pharmacy, Taipei College of Medicine, Taipei, Taiwan
1990-1995	Ph.D. - Genetics and Cell Biology, University of Minnesota Twin Cities, Minnesota, USA

Research and Professional Positions Held in Chronological Sequence

1996-2000	Post-doctoral fellow of tumor biology, University of Texas M. D. Anderson Cancer Center, Houston, Texas USA
2000-2002	Instructor, University of Texas M. D. Anderson Cancer Center, Department of Molecular and Cellular Oncology, Houston, Texas USA
2002-2007	Research-track Assistant Professor, University of Texas M. D. Anderson Cancer Center, Department of Molecular and Cellular Oncology, Houston, Texas USA
2007-2014	Tenure-track Assistant Professor, Department of Cancer Biology, University of Cincinnati College of Medicine, Cincinnati, Ohio USA
2014-2016	Associate Professor, Department of Cancer Biology, University of Cincinnati College of Medicine, Cincinnati, Ohio USA
2013-present	-Member, Cincinnati Cancer Center (CCC) -Member, University of Cincinnati Cancer Institute (UCCI)
2016-present	-Professor, Graduate Institute of Biomedical Sciences, China Medical University, Taichung City, Taiwan -Investigator, Center of Molecular Medicine, China Medical University Hospital, Taichung City, Taiwan - Adjunct Associate Professor, Department of Cancer Biology, University of Cincinnati College of Medicine, Cincinnati, Ohio USA - Adjunct Professor, Department of Biotechnology, Asia University, Taiwan
2016-2020	Program Director, China Medical University-Academia Sinica PhD Graduate Program of Translational Medicine, China Medical University, Taiwan
2016-2024	Program Director, China Medical University-Academia Sinica PhD Graduate Program of Cancer Biology and Drug Development, China Medical University, Taiwan
2016-2025	Deputy Director, Center for Molecular Medicine, China Medical University Hospital, Taichung City, Taiwan
2019-2023	Associate Dean, College of Medicine, China Medical University, Taichung City, Taiwan
2019-2025	Director, Research Center for Cancer Biology

2025-present Chair, China Medical University Hospital IACUC

Awards and Honors (past 5 years)

2021 Scholar of Global Networking Talent Plan, Ministry of Education, Taiwan
2021 Elsevier global top 2% science-wide author (current)
2022 Elsevier global top 2% science-wide author (current and career)
2022 19th National Innovation Award (top 15 out of ~500 competing teams)
2023 National Health Research Institutes (NHRI) Research Award
2024 Elsevier global top 2% science-wide author (current and career)
2024 21st National Innovation Advance Award
2025 National Science and Technology Council (NSTC) Future Tech Award
2025 Elsevier global top 2% science-wide author (current and career)
2025 22nd National Innovation Advance Award

Research Interests

My laboratory uses integrated cellular, molecular, genetic, and translational approaches to investigate mechanisms underlying human diseases. We combine mechanistic studies in cell-based systems with genetically engineered mouse models, patient-derived organoids, and clinically annotated human specimens. Through close clinical and international collaborations, this strategy enables us to define disease mechanisms, establish biologic relevance across complementary model systems, and advance discoveries toward biomarker development and therapeutic translation.

Major current research interests focus on the following areas:

1. Tumor immune microenvironment and cancer progression - We study how tumor, stromal, and immune cells interact to shape immune suppression, immune cell exhaustion, inflammatory responses, metastasis, and treatment outcome, with the goal of unveiling the underlining mechanisms and translate the knowledge to targeted therapy to improve anti-tumor immunity.
2. Tumor-selective therapeutic targeting and biomarker-guided drug development - We develop biomarkers and targeted therapies that exploit tumor-specific molecular features to improve treatment selectivity, efficacy, and safety. Our work includes antibody–drug conjugates (ADCs), antibody-based platforms, and small-molecule strategies designed to enhance therapeutic targeting, reduce off-target toxicity and overcome tumor-associated immune suppression.
3. Ovarian endocrine regulation and obesity - We investigate how ovarian steroid hormone production is regulated within specific cellular compartments of the ovary and how these endocrine programs influence systemic energy metabolism. Our work focuses on the molecular mechanisms governing estrogen biosynthesis in granulosa cells and their relevance to obesity and obesity-associated metabolic disorders.

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

Chuan-Chun Lee[1,2], Wan-Rong Wu[2], Liang-Chih Liu[3], Ting-Yi Liao[3], You-Zhe Lin[2,4], Fang-Ying Lin[2], Yi-Chun Shen[1,2], Feng-Chi Chung[4], Yuan-Liang Wang[1,5], Chih-Hao Lu[6,7,8], Wei-Chung Cheng[2,4], Wei-Chao Chang[1,2], Yi-Chuan Li[2,9], Chih-Tung Lin[2], Chung-Yu Chen[2], Sheng-Wen Chen[2], Tsung-Wei Chen[10], Hsin-An Shih[11], Steven Lin[11], I-Wen Chou[2], Chen-Yuan Lin[12,13], Chang-Fang Chiu[12,14], Shao-Chun Wang[1,2,4,15,16]*

[1]Center for Molecular Medicine, China Medical University Hospital, Taiwan, [2]Cancer Biology and Precision Therapeutics Center, China Medical University, Taiwan, [3] Division of Breast Surgery, Department of Surgery, China Medical University Hospital, Taiwan, [4]Graduate Program for Cancer Biology and Drug Discovery, China Medical University and Academia Sinica, Taiwan, [5]Graduate Institute of Biomedical Sciences, China Medical University, Taiwan, [6]Department of Biological Science & Technology, National Yang Ming Chiao Tung University, Taiwan, [7]Institute of Bioinformatics and Systems Biology, National Yang Ming Chiao Tung University, Taiwan, [8]Center for Intelligent Drug Systems and Smart Bio-Devices (IDS^{2}B), National Yang Ming Chiao Tung University, Taiwan, [9]Department of Biological Science and Technology, China Medical University, Taiwan, [10]Department of Pathology, Asia University Hospital, Asia University, Taiwan, [11]Institute of Biological Chemistry, Academia Sinica, Taiwan, [12]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taiwan, [13]School of Pharmacy, China Medical University, Taiwan, [14]Cancer Center, China Medical University Hospital, Taiwan, [15]Department of Biotechnology, Asia University, Taiwan, [16]Department of Cancer Biology, University of Cincinnati, USA

Deregulated proliferation imposes replication stress as a fundamental hallmark of cancer and an attractive therapeutic vulnerability. Yet its therapeutic translation has been limited by toxicity, resistance, and incomplete mechanistic understanding of how this liability can be exploited selectively. Recent studies have revealed a close connection between DNA damage responses and the tumor immune microenvironment, expanding the significance of replication stress beyond cancer cell–intrinsic genome maintenance. Our work addresses this emerging concept by defining a mechanism through which cancer cells sustain proliferation while evading immune surveillance. Mechanistically, our studies center on MRE11, an essential nuclease involved in DNA damage response and DNA repair. We identify MRE11 polyubiquitination as a key regulatory event that converts replication stress into an immune-activating signal. In this state, MRE11 shifts toward an endonuclease-active mode and generates cytosolic ssDNA, thereby activating the cGAS–STING–type I interferon pathway and sensitizing tumor cells to natural killer (NK) cell–mediated killing. However, cancer cell–intrinsic growth signaling counteracts this process by inducing Y211 phosphorylation of proliferating cell nuclear antigen (PCNA) within the replication machinery. Phosphorylated PCNA serves as a docking platform for a deubiquitinating enzyme, which removes ubiquitin from MRE11, suppresses its endonuclease activity, reduces cytosolic ssDNA production, and weakens immune detection. Conversely, inhibition of PCNA phosphorylation promotes recruitment of an E3 ubiquitin ligase complex, restores MRE11 polyubiquitination, and reactivates the cytosolic ssDNA–cGAS–STING–type I interferon axis. In human breast cancer, increased cytosolic ssDNA is associated with reduced Y211-phosphorylated PCNA and improved clinical outcome. In immunocompetent tumor-bearing mice and patient-derived organoids co-cultured with autologous PBMCs, targeting this deubiquitinating enzyme enhances immune-mediated tumor control, supporting the translational relevance of this pathway. Together, these findings identify a cancer cell–intrinsic escape mechanism that disconnects replication stress from anti-tumor immune surveillance. By restoring immunogenic cytosolic DNA generation and re-engaging cGAS–STING–type I interferon signaling, targeting this axis may convert tumor growth signaling from a driver of immune evasion into a therapeutic vulnerability.

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Web: https://my.nthu.edu.tw/~maplab/index.html

Education

1997-2001	B.S., Chemical Engineering, National Tsing Hua University, Taiwan
2001-2003	M.S., Chemical Engineering, National Tsing Hua University, Taiwan
2006-2012	Ph.D., Chemical Engineering, Texas A&M University, USA

Research and Professional Positions Held in Chronological Sequence

2013-2016	Postdoctoral Research Associate, Biosecurity and Public Health, Los Alamos National Laboratory, Los Alamos, New Mexico, USA
2016-2021	Assistant Professor, Department of Chemical Engineering, National Tsing Hua University, Hsinchu, Taiwan
2020-present	Joint Appointment Professor, Program of Molecular Engineering, National Tsing Hua University, Hsinchu, Taiwan
2021-2025	Associate Professor, Department of Chemical Engineering, National Tsing Hua University, Hsinchu, Taiwan
2021-present	Editor, Chemical Engineering, Taiwan Institute of Chemical Engineers
2021-present	Joint Appointment Professor, PhD Program in Biomedical Artificial Intelligence
2021-present	Joint Appointment Professor, PhD Program in Precision Medicine
2021-present	Joint Appointment Professor, Innovative Design Program
2025-present	Professor, Department of Chemical Engineering, National Tsing Hua University, Hsinchu, Taiwan
2025-present	Associate Editor, Journal of the Taiwan Institute of Chemical Engineers (IF 6.3)

Research Interests

My research focuses on microfluidic technologies for biomedical and chemical engineering applications. We develop advanced *in vitro* and *ex vivo* disease models that recapitulate 3D tissue microenvironments for personalized drug screening and precision medicine, including chemotherapy, targeted therapy, immunotherapy, and inhalation treatment. We also design integrated microfluidic diagnostic platforms for sample processing, reaction control, and rapid readout in applications such as circulating tumor cells, neonatal jaundice, and antimicrobial resistance. In parallel, we develop automated microfluidic process-control systems for continuous protein purification and apply microfluidic flow chemistry to sustainable synthesis of nanoparticles, biomaterials, and high-value chemicals.

Major Honors and Awards

2016	R&D 100 Awards
2019	R&D 100 Awards
2021	College Student Research Creativity Award (Advisor)
2021	MOST Excellent Young Scholars Award
2022	TwIChE Outstanding Chemical Engineering Article of the Year
2023	BEST Professor Shih-Yow Huang Memorial Award
2023	NSTC, Future Tech Award
2024	NSTC Taiwan Germination Program
2024	Boehringer Ingelheim 2023 Unicorn 2.0 - BioMedicine Innovation Program
2024	NTHU College of Engineering Outstanding Mentor Award
2024	National Innovation Award
2025	NTHU-YEH,KUN-MING Distinguished Young Scholar Award
2025	MOEA Technology Development Program for Academia

MedSelect: A Tumor-Microenvironment-on-Chip Platform for Functional Immunotherapy Screening and Translational Oncology

Jen-Huang Huang
黃振煌

National Tsing Hua University, Taiwan

The development of effective anticancer therapies remains constrained by the limited predictive power of conventional preclinical models. Two-dimensional cell culture systems fail to capture the spatial organization, stromal regulation, immune interactions, and molecular gradients that shape therapeutic response, whereas animal models are costly, time-consuming, and difficult to standardize across treatment settings. These limitations are particularly critical for immunotherapy and combination regimens, whose efficacy is strongly influenced by the tumor microenvironment. Despite rapid advances in cancer immunotherapy, few existing *in vitro* platforms are capable of functionally screening immunotherapy-oriented drug responses in a physiologically relevant and experimentally practical manner.

To address this challenge, we developed MedSelect, a tumor-microenvironment-on-chip platform that integrates three-dimensional tumor culture, dynamic perfusion, and spatial gradients of oxygen, nutrients, and drug exposure to reconstruct essential features of solid tumors. The platform enables region-specific analysis of therapeutic responses across heterogeneous tumor zones and supports the incorporation of stromal and immune components for evaluating microenvironment-dependent resistance and treatment sensitivity. Importantly, the significance of such a platform lies not merely in its engineering design, but in whether it can be supported by rigorous biological validation and meaningful experimental evidence. Our recent studies demonstrate that MedSelect can support functional evaluation of combination immunotherapy, preserve key features of tumor heterogeneity, and generate drug-response patterns that closely align with corresponding *in vivo* observations. Ongoing work further extends the system to patient-derived tissues, organoid-based models, PDX-derived samples, and humanized immune co-culture workflows to enhance its translational relevance.

This presentation will highlight how MedSelect has evolved from a microphysiological research platform into a data-driven and biologically validated system for functional drug evaluation, with particular emphasis on its potential in immunotherapy screening, translational cancer research, and future precision oncology applications.

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Education

1982-1986	B.S., Agricultural Chemistry, National Taiwan University, Taiwan
1988-1993	Ph.D. Cell and Developmental Biology, Harvard University, USA

Research and Professional Positions Held in Chronological Sequence

1994-1998	Postdoctoral fellow, University of Chiago, Howard Hughes Medical Institute, USA
1998-2005	Assistant Professor (tenure track), Center for Tissue Regeneration and Repair, Department of Orthopaedic Surgery, University of California-Davis, USA
2005-2007	Associate Professor (tenured), Center for Tissue Regeneration and Repair, Department of Orthopaedic Surgery, University of California-Davis, USA
2007-2009	Associate Professor (tenured), Center for Tissue Regeneration and Repair, Department of Biochemistry and Molecular Medicine, University of California-Davis
2007/5-8	Visiting scholar. Department of Molecular Medicine, Max Planck Institute for Biochemistry, Martinsreid. Germany
2009-2024	Professor (tenured), Department of Biochemistry and Molecular Medicine, University of California-Davis
2013/11-12	Visiting scholar. Institute of Biological Chemistry, Academia Sinica, Taiwan
2023/3-5	Visiting scholar. Institute of Biomedical Sciences, Academia Sinica, Taiwan
2024-present	Professor Emeritus, Department of Biochemistry and Molecular Medicine, University of California-Davis,
2024-present	YuShan Scholar, Cancer and Immunology Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan
2024-present	Distinguished Investigator & Director, Institute of Molecular and Genomic Medicine, National Health Research Institutes, Taiwan
2024-present	Visiting Professor, Department of Biochemical Science and Technology, National Taiwan University, Taiwan
2025-present	President, The Chinese Society of Cell and Molecular Biology, Taiwan

Research Interests

To understand the structure, function, and signaling pathways mediated by focal adhesions, and their roles in tissue development and human disease

Major Honors and Awards

1994-1998	Howard Hughes Medical Institute Postdoctoral fellowship
1998-1999	UC Davis new faculty research award
1999-2001	UC Davis health system research award
2001-2002, 2003-2004, 2010-2011	UC Cancer Research Coordinating Committee Award (3x)
2001-2002 2003-2004	UC Davis faculty research award (2x)
2003-2008	Shriners Hospitals Research Award
2005-2006	UC Davis Cancer Center Development Award
2008	Joan Oettinger Memorial Award
2021	The *Experimental Biology and Medicine* (EBM) Outstanding Reviewer Award
2024-2027	The Yu-Shan Fellow, Ministry of Education, Taiwan

Focal Adhesions in Human Diseases

Su Hao Lo
羅世皓

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

Focal adhesions are the transmembrane junctions linking the extracellular matrix to the cytoskeleton. This physical interaction allows cells to communicate with their outside environment and respond appropriately, leading to cell attachment, migration, proliferation, differentiation, and gene expression. TNS1 (tensin-1) is an actin-binding protein that anchors the actin cytoskeleton to focal adhesions by simultaneous interactions with actin filaments and b integrin. Being a highly phosphorylated SH2 domain-containing protein, TNS1 actively participates in a variety of signaling pathways mediated through phosphorylation cascades. Our recent studies have shown that TNS1 is able to form biomolecular condensates that are spherical, fusible, and photobleach-recoverable in cells. TNS1 condensates selectively recruit client proteins including focal adhesion components and signaling molecules to the condensates. Live-cell time-lapse studies showed phase separation of TNS1 occurs at focal adhesions. Together, our results have led us to propose that the dynamics of TNS1 condensates will help cells organize and coordinate the complex focal adhesion processing pathways in response to internal and external signaling cues.

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Education

1978-1985	M.D., Chung San Memorial College, Taichung, Taiwan.

Research and Professional Positions Held in Chronological Sequence

1984-1993	Residency, Chang Gung Memorial Hospital Linkou Branch
1993-present	Attending Physician, Department of Neurosurgery, Chang Gung Memorial Hospital
2008-2012	Chief, Division of Brain Tumor, Department of Neurosurgery, Chang Gung Memorial Hospital
2012-2014	Chief, Department of Neurosurgery, Chang Gung Memorial Hospital
2013-2020	Vice chairman, Department of Surgery, Chang Gung Memorial Hospital
2017-2020	Associate Professor, School of Medicine, Chang Gung University
2020-2024	Vice Superintendent, New Taipei City Municipal Tucheng Hospital

Research Interests

1. Neurosurgery
2. Systemic analysis of brain tumor markers
3. Development of innovate brain tumor treatment system

Major Honors and Awards

2014 Chien-Tien Hsu's Cancer Research Award
2014 Taiwan Healthcare and Agricultural Biotech industries Innovation and Excellence Awards
2015, 2019, 2021, 2023, 2024, 2025 Academic Research Innovation
2016 Outstanding Innovative Research Grant, National Health Research Institutes
2017 Award for Excellent Contributions in Technology Transfer, Ministry of Science and Technology
2021 Taiwan Medical Role Model Award
2022 Medical Charity Award, New Taipei City Government
2023 the Tech Innovation Excellence Award
2025 Outstanding Research Award, the National Science and Technology Council

Developing Neuronavigation-Guided Focused Ultrasound for Brain Therapy: From Concept to Clinical Trials

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魏國珍

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Malignant glioma remains one of the most devastating human cancers, with poor prognosis despite maximal surgical resection followed by chemoradiotherapy. One of the major obstacles in neuro-oncology is the blood–brain barrier (BBB), which severely limits the delivery of therapeutic agents into the brain. Focused ultrasound (FUS) combined with microbubbles has emerged as a promising strategy to transiently and reversibly open the BBB in a targeted and noninvasive manner.

Over the past decade, our team has developed a neuronavigation-guided FUS platform for brain therapy and successfully translated this technology from laboratory research into clinical application. Preclinical studies from our group demonstrated that FUS-mediated BBB opening can enhance the delivery and therapeutic efficacy of chemotherapy, targeted therapy, and radiotherapy in malignant glioma models. These findings supported the advancement of FUS-BBB opening into clinical studies for recurrent glioblastoma.

Our translational program progressed from a first-in-human phase I safety trial to a phase II clinical study combining FUS-BBB opening with bevacizumab therapy. Building upon favorable safety and feasibility outcomes, our multicenter phase III clinical trial is currently ongoing. Throughout this translational journey, our team has encountered and addressed multiple challenges involving device development, treatment planning, regulatory approval, clinical trial design, and multicenter implementation.

Beyond drug delivery, our recent efforts have further expanded into integrating FUS-mediated BBB opening with emerging therapeutic strategies, including immunotherapy and sonodynamic therapy, aiming to further improve treatment efficacy for malignant brain tumors. The successful clinical translation achieved by our team highlights the potential of focused ultrasound to become a novel therapeutic platform and potentially a fifth modality in the multimodal treatment of malignant glioma.

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Education

1993-1997	BSc, Department of Chemistry, National Chung Cheng University, Taiwan.
1997-1999	MSc, Institute of Biochemical Sciences, National Taiwan University, Taiwan.
2002-2006	PhD, The Wellcome Trust Cancer Research UK Gurdon Institute, University of Cambridge, UK.

Research and Professional Positions Held in Chronological Sequence

2001-2002	Teaching Instructor, Institute of Biochemical Sciences, National Taiwan University, Taiwan.
2002-2006	PhD student, Supervised by Dr. Enrique Amaya, The Wellcome Trust/CR UK Gurdon Institute, University of Cambridge, UK
2007-2012	Postdoctoral Fellow, Supervised by Dr. Hynek Wichterle, Columbia University, USA.
2012-2019	Assistant Research Fellow, Principal Investigator, Institute of Molecular Biology, Academia Sinica, Taiwan.
2019-2023	Associate Research Fellow, Principal Investigator, Institute of Molecular Biology, Academia Sinica, Taiwan.
2023-present	Full Research Fellow, Principal Investigator, Institute of Molecular Biology, Academia Sinica, Taiwan.
2025-present	Deputy Director, Institute of Molecular Biology, Academia Sinica, Taiwan.

Research Interests

The focus of research in my laboratory is to elucidate how neurons establish individual identity in the developing nervous system and why only specific neuron subtypes are vulnerable in neurodegenerative diseases. We tackle these questions by studying non-coding RNAs and their roles during motor neuron (MN) generation and degeneration. My laboratory employs MNs generated from mouse and human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), as well as mouse/chicken animal models to investigate MN development and disease. We have developed a series of stem cell lines and animal models to study the functions of microRNAs and lncRNAs by “gain-of-function” and “loss-of-function” approaches. Apart from elucidating the basic molecular mechanisms underlying neuronal diversity specification during central nervous system development, we use stem cells to study MN diseases. In particular, we are engaged in establishing patient-specific iPSC-based models of Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS). We perform single cell multiomics on healthy and ALS iPSC-derived MNs to functionally characterize non-coding RNA pathologies in MNs. I am also a core member of the

Neuroscience Program and RNA Program in Academia Sinica, which provide strong and stable consortia for inter-institutional collaborations. In summary, I employ multidisciplinary approaches, from *in vitro* stem cells to *in vivo* mouse models, to study MN development and degeneration.

Major Honors and Awards

2000	Presidential Award in NCCU
2002-2005	Taiwan International PhD Scholarship
2002-2006	The Wellcome Trust Scholarship
2008-2009	Taiwan National Science Council Postdoctoral Fellowship
2012-2015	Taiwan National Science Council Talented Investigator Fellowship
2018-2022	Academia Sinica Career Development Award
2018	Academia Sinica Junior Research Investigators Award
2019	The 15th TienTe Lee Award-Young Scientists, TienTe Lee Biomedical Foundation
2019	Outstanding Alumni Award of National Chung Cheng University
2020	MOST Outstanding Research Award
2020-2025	MOST Frontier Science Research Program
2021-2023	Academia Sinica Presidential Scholars Program
2023	NHRI multiple time awardee
2024	NSTC Outstanding Research Award
2026-2030	Academia Sinica Investigator Project Grant
2025-2026	Ewha Global Fellow, Ewha Womans University, Korea

Sertm2 Is A Conserved Micropeptide that Promotes GDNF-mediated Motor Neuron Subtype Specification

Fang-Yu Hsu[1,2], Ya-Ping Yen[1], Hung-Chi Fan[1], Mien Chang[1], Jun-An Chen[1,2,3]
許芳瑜, 顏雅萍, 范宏綦, 張綿, 陳俊安

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Neuroscience Program of Academia Sinica, Academia Sinica, Taiwan.

Small open-reading frame-encoded micropeptides within long noncoding RNAs (lncRNAs) are often overlooked due to their small size and low abundance. However, emerging evidence links these micropeptides to various biological pathways, though their roles in neural development and neurodegeneration remain unclear. Here, we investigate the function of murine micropeptide Sertm2, encoded by the lncRNA A730046J19Rik, during spinal motor neuron (MN) development. Sertm2 is predicted to be a conserved transmembrane protein found in both mouse and human, with subcellular analysis revealing that it is enriched in the cytoplasm and neurites. By generating C terminally Flag-tagged Sertm2 and expressing it from the A730046J19Rik locus, we demonstrate thatthe Sertm2 micropeptide localizes in spinal MNs in mice. The GDNF signaling-induced Etv4+ motor pool is impaired in Sertm2 knockout mice, which display motor nerve arborization defects that culminate in impaired motor coordination and muscle weakness. Similarly, human SERTM2 knockout iPSC-derived MNs also display reduced ETV4+ motor pools, highlighting that Sertm2 is a novel, evolutionarily conserved micropeptide essential for maintaining GDNF-induced MN subtype identity.

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Education

1988-1995	Taipei Medical University, Taiwan

Research and Professional Positions Held in Chronological Sequence

1998-1999	Chief Resident Physician, Department of Neurology, Neurologic Institute Taipei Veterans General Hospital
1999-2002	Fellow, Epilepsy Section, Department of Neurology, Neurologic Institute, Taipei Veterans General Hospital
2001.07-2002.01	Visiting researcher, Neurosurgery Department, Tohoku University, Sendai, Japan
2002.3 -present	Attending doctor, Epilepsy Section, Department of Neurology, Neurologic Institute, Taipei Veterans General Hospital
2009.07-2009.12	Observer, Comprehensive Epilepsy Center, New York University Langone
2011.08-2021.07	Assistant Professor, Neurology, National Yang-Ming University
2018.02- 2024.02	Section Chief, Epilepsy section, Neurologic Institute, Taipei Veterans General Hospital
2021.08~present	Associate Professor, Neurology, National Yang Ming Chiao Tung University

Research Interests

women's issues, epilepsy surgery, neuromodulation and intracranial EEG and published her works in journals of associated fields.

Major Honors and Awards

2021	XXV Moscow International Salon of Inventions and Innovative Technologies 「ARCHIMED 2021」- Gold Medal
2022	Taiwan Innotech Exop- Gold Medal Award
2022	International Innovation and Invention Competition- Gold Medal
2022	Certificate of The 21st National Innovation Award- Clinical Research Category
2023	NARLabs R&D Service Platform Achievement Awards- Honorable Mention

Toward Precision Neuromodulation in Epilepsy: Mapping and Modulating the Epileptogenic Network

Hsiang-Yu Yu
尤香玉

Neurology department, Taipei Veterans General Hospital and
National Yang Ming Chiao Tung University, Tawan

Over the past two decades, neuromodulation has become an increasingly important therapeutic strategy in neurology, with major advances in the treatment of drug-resistant epilepsy (DRE). Implantable neuromodulation therapies, including vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS), have been incorporated into clinical practice and have demonstrated meaningful seizure reduction, with at least half of treated patients achieving a ≥50% reduction in seizure frequency in well-designed clinical studies and real-world data. In parallel, less invasive or non-implantable approaches, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and low-intensity focused ultrasound stimulation (LIFUS), have also shown potential antiseizure effects in case series and early-phase studies, although large-scale controlled trials remain limited. Neuromodulation strategies differ substantially in their mechanisms and targeting concepts. VNS, rTMS, and tDCS generally modulate broader cortical or subcortical networks, and the stimulation targets are relatively similar across patients. In contrast, DBS, RNS, and LIFUS require more individualized target selection before treatment. These approaches aim to modulate epileptogenic foci or critical hubs within the epileptic network, and the optimal targets may vary considerably between patients. Therefore, accurate identification of stimulation targets has become a central issue in modern epilepsy neuromodulation.

Determination of modulation targets relies on multimodal neuroimaging and electrophysiological information, particularly intracranial EEG. These techniques allow clinicians to better define the seizure onset zone, propagation pathways, and key epileptic network nodes. This concept has become an important research focus for comprehensive epilepsy surgery and neuromodulation programs worldwide.

In Taiwan, RNS has not yet been introduced into routine clinical practice. Our team has accumulated clinical and research experience in DBS and LIFUS for patients with DRE. In this presentation, I will share our experience in using SEEG and advanced neuroimaging techniques to identify individualized neuromodulation targets, and present our preliminary clinical results and future perspectives on precision neuromodulation for epilepsy.

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Education

1995-2000	Ph.D. University of Washington, Seattle, USA

Research and Professional Positions Held in Chronological Sequence

2000-2005	Senior Fellow/Acting Instructor, Division of Neuropathology, Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA.
2005-2011	Assistant Investigator, Division of Mental Health and Addiction Medicine, National Health Research Institutes, Zhunan, Taiwan.
2011-2022	Associate Investigator, Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan, Taiwan.
2022-present	Investigator, Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan, Taiwan.

Research Interests

My research focuses on understanding the roles of glial cells in the central nervous system and developing therapeutic strategies for neurodegenerative diseases, particularly Alzheimer's disease (AD). AD is a highly complex and multifactorial disorder involving amyloid pathology, tauopathy, neuroinflammation, vascular dysfunction, and impaired brain homeostasis. Despite extensive research, the precise mechanisms underlying disease initiation and progression remain incompletely understood, limiting the development of effective disease-modifying therapies.

A central theme of my work is the investigation of microglial and astrocytic functions during neurodegeneration. Increasing evidence suggests that glial activation is highly dynamic and context-dependent. Activated glial cells may exert beneficial effects by facilitating amyloid clearance, supporting neuronal survival, and maintaining brain homeostasis. However, chronic or maladaptive glial activation can amplify neuroinflammation, disrupt blood–brain barrier (BBB) integrity, impair synaptic function, and accelerate neurodegeneration. Therefore, understanding how to fine-tune glial activation toward protective rather than detrimental states is critical for developing next-generation AD therapies.

Importantly, AD pathology is believed to begin decades before the onset of clinical symptoms. Early alterations in neuroinflammation, BBB dysfunction, and neuronal stress may occur long before overt cognitive decline becomes detectable. My research aims to identify early pathological mechanisms and develop therapeutic approaches that enhance brain resilience while interrupting the self-reinforcing cycles of glia-mediated neuroinflammation.

To address these challenges, our laboratory has been developing novel multi-target therapeutic strategies, including combination therapy using small molecules and antibody-based therapies. In particular, we developed NP106, a multifunctional anti-amyloid antibody designed not only to

enhance amyloid clearance, but also to modulate glial activation, suppress excessive neuroinflammation, and preserve neurovascular homeostasis. Our studies further integrate spatial transcriptomics, peripheral blood mononuclear cells (PBMC) RNA sequencing, blood-based biomarkers, and animal models to characterize therapeutic responses and to identify biomarkers and molecular pathways associated with brain resilience to neurodegeneration.

Another interest of my research is apolipoprotein E4 (APOE4), the strongest genetic risk factor for late-onset AD. Emerging evidence suggests that APOE4 may not simply promote amyloid accumulation in the pathogenesis of AD or increase the risk of amyloid-related imaging abnormalities (ARIA) during AD immunotherapy, but instead predispose the brain to chronic neurovascular vulnerability and maladaptive immune responses. Interestingly, many APOE4 carriers remain cognitively intact throughout life, indicating that APOE4 alone is insufficient to determine neurodegenerative outcomes and that additional inflammatory, vascular, and environmental stressors are likely required to trigger disease progression. My work seeks to elucidate how APOE4 interacts with glia-mediated neuroinflammation, BBB dysfunction, and PBMC immunity to influence disease susceptibility, therapeutic responsiveness, and cognitive resilience.

Ultimately, my long-term goal is to develop precision medicine strategies for early AD diagnosis through the establishment of a blood-based multidimensional composite prediction index, as well as safer and more efficient disease-modifying therapies with reduced risk of ARIA, by integrating glial biology, APOE4-associated vulnerability, and neurovascular dysfunction into a comprehensive therapeutic framework.

Major Honors and Awards

2025 The 22nd National Innovation Award (Academic Innovation Award)

APOE4 and the Failure of Brain Resilience in Alzheimer's Disease

Feng-Shiun Shie
謝奉勳

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Alzheimer's disease (AD) is the leading cause of dementia in older adults. Although recently approved anti-amyloid-β (Aβ) immunotherapies provide modest clinical benefits, their efficacy varies substantially among patients and is accompanied by amyloid-related imaging abnormalities (ARIA), particularly in carriers of the apolipoprotein E ε4 (APOE4) allele. APOE is a key lipid transport protein, mediating cholesterol and phospholipid trafficking among lipoprotein particles to support neuronal metabolism, synaptic plasticity, membrane repair, and tissue homeostasis. APOE4 isoform disrupts these functions and promotes AD pathology, mitochondrial dysfunction, oxidative stress, neuroinflammation, blood-brain barrier (BBB) disruption, and dysregulated lipid metabolism. Consequently, APOE4 allele is the strongest genetic risk factor for late-onset AD.

An enduring paradox in AD research is that many APOE4 carriers remain cognitively intact throughout life, whereas others rapidly develop dementia. This discrepancy suggests that APOE4 does not inevitably determine disease onset but instead lowers the brain's capacity to tolerate and compensate for accumulating pathological insults. Accordingly, increasing evidence supports a conceptual shift from viewing APOE4 allele solely as a genetic risk factor to recognizing it as a critical regulator of brain resilience—the ability to preserve cognitive function despite age- or disease-related pathological changes. For APOE4 carriers, this resilience may be more easily compromised by the long-term accumulation of oxidative stress, impaired lipid metabolism, cerebrovascular dysfunction, BBB disruption, and neuroimmune activation. As these compensatory mechanisms gradually fail, the brain becomes increasingly vulnerable, eventually reaching a critical threshold that accelerates cognitive decline and the progression to clinical dementia.

This resilience-based framework also offers new insights into therapeutic responses and may explain why APOE4 carriers, particularly homozygotes, exhibit a markedly higher susceptibility to ARIA following anti-Aβ immunotherapy than individuals with other APOE genotypes. Accumulating evidence suggests that pre-existing impairment of BBB integrity and neurovascular function may constitute fundamental determinants of ARIA susceptibility. These observations underscore the importance of elucidating the biological mechanisms that maintain neurovascular stability and brain resilience to enable the development of safer, more effective, and multi-target disease-modifying therapies. Collectively, recent research advances have redefined the biological functions of APOE4 beyond the scope of amyloid metabolism and highlighted impaired brain resilience as a central mechanism linking genetic susceptibility to disease progression and treatment vulnerability.

Importantly, the pathological cascade of AD begins one to two decades before the onset of clinical dementia, indicating that the progressive loss of brain resilience precedes overt cognitive symptoms by many years. This prolonged preclinical phase provides a critical opportunity for early diagnosis, precision risk stratification, and timely intervention before compensatory mechanisms are exhausted. Emerging blood-based biomarkers that capture APOE4-associated resilience failure and neurovascular dysfunction may therefore complement conventional amyloid and tau biomarkers by reflecting the early biological processes underlying disease progression. Such biomarkers have the potential to improve early AD diagnosis, predict therapeutic response and ARIA susceptibility, facilitate treatment monitoring, and enable more precise patient stratification. Ultimately, understanding why some APOE4 carriers maintain brain resilience whereas others develop dementia may shift the focus of AD research from simply reducing pathological burden toward preserving brain resilience, thereby opening new avenues for precision diagnostics and next-generation disease-modifying therapies.

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Education

2001	M. D., National Cheng-Kung University
2013	Ph.D., National Yang-Ming Chiao Tung University

Research and Professional Positions Held in Chronological Sequence

2002~2008	Residency and fellowship, cardiology and cardiac electrophysiology, Internal Medicine Department, Taipei Veterans General Hospital, Taiwan
2008~2009	Attending Physician, Taipei Medical University Hospital, Taiwan
2009~	Attending Physician, Taipei Veterans General Hospital, Taiwan
2013~2014	Post-doctor fellow, Smidt Heart Institute, Cedar Sinai Medical Center, USA
2019~2021	Associate Professor, National Yang Ming Chiao Tung University, Taiwan
2022~	Joint associate research fellow, Academia Sinica, Taiwan
2022~2023	Professor, Faculty of Medicine, National Yang Ming Chiao Tung University, Taiwan
2023~	Professor, Institute of Biopharmaceutical Sciences, National Yang Ming Chiao Tung University, Taiwan

Research Interests

1. Cardiac reprogramming and pacemaker cell generation
2. Cardiac electrophysiology and arrhythmias
3. Stem cell biology and cardiac regeneration
4. Human induced pluripotent stem cell (iPSC)-derived cardiomyocytes
5. Artificial intelligence applications in cardiovascular research and digital health innovations
6. Genetic testing and precision medicine in cardiovascular diseases

Major Honors and Awards

2009	Young Investigator Award, Taiwan Society of Cardiology
2010	Young Investigator Award, The 11th US-Japan-Asia Dialogue Symposium on Cardiovascular Diseases
2015	Benjamin N. Chiang Prize
2017	Best Article Award, Acta Cardiologica Sinica
2018	Paul Dudley White International Scholar Award, American Heart Association
2021	Outstanding Young Alumni Award, National Cheng Kung University
2022	FutureTech Award
2022	Wu Ho-Su Medical Research Award

2022	Physician Innovation Award, Taipei Veterans General Hospital
2022	Investigator High Impact Factor Award, Taipei Veterans General Hospital
2023	Outstanding Research Award, National Science and Technology Council, Taiwan
2023	Award of Outstanding Paper, The 19th National Taiwan University System Collaborative Research Project
2023	National Innovation Award
2024	World's Top 2% Scientists (Cardiovascular System & Hematology), Stanford University based on Scopus Data
2025	World's Top 2% Scientists (Cardiovascular System & Hematology), Stanford University based on Scopus Data

The Pulse of Life: From Sinoatrial Node Pathogenesis to Biological Pacing

Yu-Feng Hu
胡瑜峰

1. Institute of Biopharmaceutical Sciences, National Yang Ming Chiao Tung University, Taiwan
2. Cardiovascular Center, Taipei Veterans General Hospital, Taiwan
3. Institute of Biomedical Sciences, Academia Sinica, Taiwan

Electrical impulses generated by cardiac pacemaker cardiomyocytes initiate cardiac contraction, sustain blood pumping, and maintain life. When pacemaker activity fails, severe bradyarrhythmia may lead to syncope, cardiac arrest, or dependence on electronic pacemakers. Although implantable electronic devices remain the standard therapy, device-related complications continue to motivate the development of hardware-free biological pacing strategies. This presentation will introduce translational studies on sinoatrial node pathogenesis, metabolic remodeling, silk fibroin–induced transdifferentiation, and hiPSC-derived pacemaker therapy. Current findings suggest that sinoatrial node dysfunction is not merely an electrical disorder, but is closely associated with impaired energetic regulation, aging-related pacemaker cell vulnerability, and metabolic remodeling. To facilitate therapeutic development and disease modeling, a silk fibroin hydrogel–based pacemaker cardiomyocyte platform has been developed that may serve both as an *in vitro* model for disease and toxicity evaluation and as a strategy for *in situ* biological pacemaker generation. The in-situ silk fibroin biological pacemaker has demonstrated functional pacing activity in preclinical large-animal models and is advancing toward translational application. In parallel, hiPSC-derived pacemaker cardiomyocyte therapies and disease prediction platforms are being developed to advance precision management and biological rhythm restoration for bradyarrhythmia.

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Education

2002-2006	B.S., Medical Biotechnology, Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University, Taiwan
2007-2009	M.S., Institute of Biophotonics Engineering, National Yang-Ming University, Taiwan
2010-2014	Dr. rer. nat., Pharmacology for Natural Sciences, Ludwig-Maximilians-Universität München, Germany Dissertation: summa cum laude

Research and Professional Positions Held in Chronological Sequence

2014-2020	Postdoctoral Fellow, Department of Pharmacy, Ludwig-Maximilians-Universität München, Germany
2021-present	Assistant Professor, Department of Clinical Laboratory Sciences and Medical Biotechnology, College of Medicine, National Taiwan University, Taiwan

Research Interests

My research focuses on endolysosomal ion channels and their roles in organelle physiology and disease. By combining organelle patch-clamp electrophysiology, calcium nanodomain imaging, pharmacology, and cell biology, my laboratory investigates how ion channels regulate lysosomal excitability, endolysosomal trafficking, host-pathogen interactions, neuroimmune responses, and disease-associated cellular phenotypes.

Major Honors and Awards

2010-2013	Bavarian Research Foundation PhD Scholarship, Bavarian Research Foundation, Germany
2014	Oskar-Karl-Forster-Stipendium Doctoral Dissertation Award, Ludwig-Maximilians-Universität München, Germany
2015	AbbVie Promotionspreis, Best Dissertation of the Year Award, Department of Pharmacy, Ludwig-Maximilians-Universität München, Germany
2021	Special Outstanding Talent Award, National Taiwan University, Taiwan

Organelle Patch-Clamp Approaches to Study Endolysosomal Ion Channels in Disease

Cheng-Chang Chen
陳政彰

Department of Clinical Laboratory Sciences and Medical Biotechnology,
National Taiwan University, Taiwan

Endosomes and lysosomes are increasingly recognized as dynamic signaling organelles that regulate trafficking, degradation, immunity, infection, metabolism, neurodegeneration, and lysosomal disorders. Their functions depend critically on ionic homeostasis, which is controlled by ion channels and transporters located on endolysosomal membranes. Compared with plasma membrane ion channels, however, endolysosomal ion channels remain technically challenging to investigate because their activity occurs within intracellular organelles that are not readily accessible by conventional electrophysiological approaches.

Organelle patch-clamp electrophysiology provides a direct approach to measure ion channel activity on enlarged endosomes and lysosomes. This technique enables functional assessment of channel gating, ion selectivity, conductance properties, and pharmacological regulation in intracellular membranes. By combining organelle electrophysiology with calcium imaging, cell biology, and disease-relevant models, our studies aim to define how endolysosomal ion channels shape organelle function and disease-associated cellular phenotypes.

This presentation will highlight recent applications of organelle patch-clamp approaches to two-pore channels and TRPML channels, with particular emphasis on lysosomal excitability, endolysosomal trafficking, host-pathogen interactions, and neuroimmune regulation. Recent findings on the post-translational regulation of lysosomal TPC2 will be discussed as an example of how direct electrophysiological measurements can reveal mechanisms that are difficult to resolve by imaging or biochemical approaches alone. Together, these studies support endolysosomal ion channels as underexplored intracellular regulators and potential therapeutic targets in human disease.

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Web: https://www.genomics.sinica.edu.tw/cmhu

Education

1999-2003	B.S., Department of Life Science, Chung Shan Medical University, Taiwan
2003-2005	M.S., Graduate Institute of Biochemistry and Molecular Biology, National Taiwan University, College of Medicine, Taiwan
2006-2010	Ph.D., Graduate Institute of Biochemistry and Molecular Biology, National Taiwan University, College of Medicine, Taiwan

Research and Professional Positions Held in Chronological Sequence

2010-2012	Postdoctoral Research Fellow, Graduate Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taiwan
2012-2013	Postdoctoral Research Fellow, Department of Biological Chemistry, School of Medicine, University of California, Irvine, USA
2013-2014	Postdoctoral Research Fellow, Genomics Research Center, Academia Sinica, Taiwan
2014-2019	Assistant Research Specialist, Genomics Research Center, Academia Sinica, Taiwan
2016-present	Adjunct Assistant Professor, Graduate Institute of Biomedical Sciences, China Medical University, Taiwan
2019-present	Assistant Research Fellow, Genomics Research Center, Academia Sinica
2021-present	Adjunct Assistant Professor, Graduate Institute of Biochemistry and Molecular Biology, National Yang-Ming Chiao Tung University, Taiwan

Research Interests

- **Translational Cancer Biology & TME:** Elucidating the molecular drivers of pancreatic ductal adenocarcinoma (PDAC) initiation, focusing on glycosylation (O-GlcNAcylation & N-glycan remodeling) and critical signaling networks (IL-17B/IL-17RB axis, Activin A).
- **AI-Driven Metabolomics & Early Diagnostics:** Pioneering non-invasive, high-resolution ^{1}H NMR-based multimodal machine learning platforms (e.g., PanMETAI) to translate untargeted metabolic profiling into high-precision clinical screening tools.
- **Pathogenic Metabolism & The Gut-Liver Axis:** Pathogenic Metabolism & The Gut-Liver Axis: Expanding metabolomic frameworks beyond oncology to investigate systemic metabolic disorders, such as pediatric steatotic liver disease (SLD). Utilizing urine metabolomics, this

research establishes microbiota-derived metabolic alterations not merely as diagnostic biomarkers, but as active pathogenic drivers of hepatic lipid dysregulation.

- **Targeted Therapeutics for Pancreatic Cancer:** Designing novel interventions to disrupt tumor microenvironment (TME) communication (e.g., ACK900 for N-glycan biosynthesis inhibition). Advancing precision medicine by targeting the IL-17RB/MLK4 interaction through structure-homology-designed cyclic peptides, high-throughput screening (HTS) of small-molecule inhibitors, and AI-driven compound optimization.

Major Honors and Awards

2008	Excellence Award The first session of the Merck Award for young biotech
2008	Excellence Award National Taiwan University Graduate Award for outstanding work
2010	Foundation for The Advancement of Outstanding Scholarship travel award for attending Gordon Research Conference meeting “Mechanisms & Models of Cancer at CSHL, New York, USA.
2011	NSC (Taiwan) travel award for attending Keystone Symposia “Genomic Instability and DNA Repair at the Keystone Resort, Keystone, Colorado, USA.
2014	Academia Sinica Postdoctoral Research Fellowship Award, Taiwan.
2019	Juei-Low Sung Foundation Distinguished Thesis Award, Taiwan.
2019	One of the Selected Scientific Research papers, Academia Sinica, Taiwan.
2020	Top Ten Scientific Research Disruptive Innovation Papers Award, Taiwan.
2021	Outstanding Scholar, Department of Biomedical Sciences, Chung Shan Medical University 2021
2022, 2023	One of the Selected Scientific Research papers, Academia Sinica, Taiwan.

Translating Urine Metabolomics into Diagnostics: Isobutyric Acid and Valine as Early Pathogenic Biomarkers for Pediatric Steatotic Liver Disease

Dan-Ni Wu[1], Chin-Chun Chang[1], Li-Wen Lee[2,3*], Chun-Mei Hu[1*]
吳丹霓[1]、張謹淳[1]、李莉文[2,3*]、胡春美[1*]

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Steatotic liver disease (SLD) is a rapidly growing global health challenge that can progress to severe complications, including steatohepatitis, cirrhosis, and hepatocellular carcinoma. Driven by the rising epidemic of childhood obesity—the primary risk factor—SLD has become a critical pediatric concern, affecting approximately 13% of the general pediatric population and up to 47% of obese children. While early-stage pediatric SLD is highly reversible, timely intervention is critically hindered by the lack of effective, non-invasive diagnostic tools. Here, using clinically relevant mouse models coupled with pH-dependent urine metabolomics, we identify a robust, non-invasive biomarker signature for SLD. In a clinical validation cohort of 218 children, a two-metabolite panel comprising isobutyric acid and valine exhibited outstanding diagnostic accuracy (AUC 0.955), retaining exceptionally high sensitivity even for mild, early-stage disease (AUC 0.967). Crucially, we trace the origin of this distinct metabolic signature to gut microbiota dysbiosis, specifically identifying the enrichment of *Lactobacillus* and *Clostridium*. Beyond their diagnostic utility, mechanistic evaluation reveals that these microbiota-associated metabolites actively promote hepatocellular lipid accumulation by driving de novo lipogenesis. This implicates isobutyric acid and valine as pathogenic drivers of SLD, rather than passive bystanders. Ultimately, this study not only establishes a powerful, non-invasive urine screening strategy for pediatric SLD, but also links gut microbiota-driven urinary metabolic alterations to hepatic lipid dysregulation, providing novel insights into SLD pathogenesis and identifying promising targets for clinical intervention.

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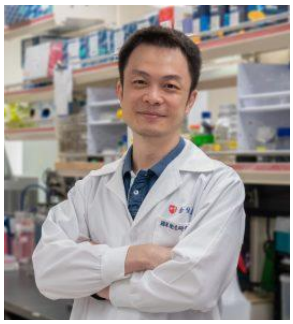

Education

1995-1999	B.S., Medical Technology, Taipei Medical University, Taiwan
1999-2001	M.S., Microbiology and Immunology, National Defense Medical Center (NDMC), Taiwan
2001-2006	Ph.D., Life Sciences, NDMC/NHRI/Academia Sinica, Taiwan

Research and Professional Positions Held in Chronological Sequence

2007-2013	Postdoctoral Research Fellowship, Virology, Institute of Biomedical Sciences, Academia Sinica, Taiwan
2014-2015	Research Assistant Professor, Department of Medical Laboratory Science and Biotechnology, National Cheng Kung University (NCKU), Taiwan
2015-2016	Research Assistant Professor, Department of Microbiology and Immunology, NCKU, Taiwan
2017-2022	Assistant Investigator, National Institute of Infectious Diseases and Vaccinology (NIIDV), NHRI, Taiwan Adjunct Assistant Professor, Department of Microbiology and Immunology, NCKU, Taiwan
2022-present	Associate Investigator, NIIDV, NHRI, Taiwan Associate Professor (Joint Appointment), Department of Microbiology and Immunology, NCKU, Taiwan

Research Interests

Molecular virology, RNA biology, innate immunity, and virus-host interactions

Major Honors and Awards

2008-2009	The Academia Sinica Postdoctoral Fellowship Award
2013	Postdoctoral Fellow Outstanding Publication Awards, National Science Council of Taiwan
2021	Research Project for Excellent Young Scholars, Ministry of Science and Technology, Taiwan
2025	The 22nd National Innovation Award, Taiwan
2025	Moderna Taiwan mRNA Innovation Awards

Making RNA circular: Wrapping the Messenger in a Closed RNA

Chia-Yi Yu
余佳益

National Institute of Infectious Diseases and Vaccinology,
National Health Research Institutes, Taiwan

The therapeutic potential of RNA is limited by the instability of linear transcripts, especially in application circumstances requiring durable protein expression or sustained antiviral activity. Circular RNA (circRNA) could be a potential solution as mRNA2.0, given its covalently closed structure, which resists degradation. However, broader use of circRNAs is limited by technical challenges in RNA circularization, including low production efficiency, heterogeneous products, and unwanted RNA byproducts. Here, we describe a *cis*-acting ligase ribozyme (RzL)-mediated circularization platform autonomously converting linear RNA precursors into highly pure circRNAs with much higher yield and no RNA byproduct formation. We used this strategy to generate IRES-containing circRNAs that direct the expression of antiviral proteins in cultured cells, resulting in broad-spectrum antiviral activity. In parallel, circRNAs encoding Cas13 specifically target and degrade viral RNA, showing the programmability of this system. Regardless of the RNA application, our RzL-mediated circRNA production system overcomes current manufacturing barriers, making it easier than ever. This work supports the development of circRNA beyond RNA vaccines, extending toward antiviral therapeutics, programmable RNA-based interventions, and broader biomedical applications.

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Education

1980-1987	M.D., Chung-Shan Medical & Dental College, Taiwan
1992-1993	M.O.H., Occupational Health, Harvard School of Public Health, U.S.A.
1993-1997	Sc.D., Occupational & Environmental Health, Harvard School of Public Health, U.S.A.

Research and Professional Positions Held in Chronological Sequence

2014-2023	Director, Research Center for Precision Environmental Medicine, Kaohsiung Medical University (KMU), Kaohsiung, Taiwan
2019-2025	Distinguished Professor, KMU, Kaohsiung, Taiwan
2017-present	Chair, Consortium of Taiwan Maternal and Infant Cohort Study, Taiwan
2014-present	Attending Physician & Physician Scientist, Department of Family Medicine, Kaohsiung Medical University Hospital, KMU, Kaohsiung, Taiwan
2014-present	Professor, PhD Program in Environmental & Occupational Medicine, KMU, Taiwan

Research Interests

Molecular Epidemiology, Environmental Health & Occupational Medicine, Community Medicine

Major Honors and Awards

2018	Outstanding Research Award, Ministry of Science and Technology
2019	Contributing Award of Food Safety, Taiwan Food Safety and Victims' Rights Promotion Association
2021-2024	World's Top 2% Scientists
2022	"Bronze Medal" of National Biotechnology and Medicine Care Quality, Title: "Using a novel and simplified improved oil fume filter barrel to reduce pollution and lower the potential risk of lung adenocarcinoma among the population"
2023	Award of Symbol of National Quality or Safety and Quality (SNQ) Title: "Health for All: Sustainable social action and innovative services to solve daily-environmental issues of phthalates and melamine

Plastic Pollution and Kidney Health: From RAPIT to TMICS and Beyond

Ming-Tsang Wu
吳明蒼

PhD Program in Environmental and Occupational Medicine,
Kaohsiung Medical University, Taiwan

A major public health crisis emerged in Taiwan in 2011 when phthalates, particularly di-(2-ethylhexyl) phthalate (DEHP), were intentionally added as substitute emulsifiers to a wide range of food products, including sports drinks, nutritional supplements, and probiotics commonly consumed by children and adolescents. Similar to the 2008 melamine-contaminated milk incident in China, this food scandal raised serious concerns regarding exposure to plastic-related environmental chemicals during vulnerable developmental periods. In response, two nationwide cohorts were established around 2012: the Risk Assessment of the Phthalate Incident in Taiwan (RAPIT) and the Taiwan Maternal and Infant Cohort Study (TMICS). These cohorts, collaboratively developed by scientists from northern, central, southern, and eastern Taiwan, were designed to investigate the health effects of environmental chemical exposures, particularly phthalates and melamine, arising from both the food scandal-related high-level exposures and everyday environmental exposures in pregnant women and children. In this presentation, I will introduce the 2011 Taiwan food scandal, describe the establishment and design of the RAPIT and TMICS cohorts, and summarize our findings on the nephrotoxic effects of phthalates and melamine in pregnant mothers and children. Furthermore, we extended this research to another vulnerable population, patients with early-stage chronic kidney disease (CKD stages 1-3), using a prospective cohort design to evaluate the combined effects of phthalates and melamine on adverse kidney outcomes, including doubling of serum creatinine and progression to end-stage kidney disease. The anticipated findings from these studies may provide important scientific evidence to support policymakers in establishing evidence-based public health guidelines and regulatory standards for environmental chemical exposure.

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Education

1990-1997	M.D., National Taiwan University, Taipei, Taiwan
2004-2005	Master of Public Health in Biostatistics and Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
2005-2008	Doctor of Science in Epidemiology, Harvard School of Public Health, Boston, USA

Research and Professional Positions Held in Chronological Sequence

1997-1999	Second Lieutenant, Army
1999-2004	Resident Physician in Internal and Emergency Medicine, National Taiwan University Hospital (NTUH)
2008-2010	Post-doctoral Fellow, Massachusetts General Hospital, Harvard Medical School
2010-2013	Assistant Professor of Epidemiology, Division of Epidemiology, Human Genetics and Environmental Health Sciences, University of Texas School of Public Health
2014-2015	Assistant Professor of Emergency Medicine, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School
2015-present	Attending Physician, Department of Emergency Medicine, NTUH
2015 - 2022	Assistant Professor, Department of Emergency Medicine, College of Medicine, National Taiwan University
2022-present	Director of Emergency Medicine Clerkship, NTUH
2023-present	Associate Professor, Department of Emergency Medicine, College of Medicine, National Taiwan University
2024-present	Deputy Director of the NTUH Integrated Medical Data Center (NTUH iMDC)
2025-present	Deputy Director of the NTUH Center for AI Impact Evaluation

Research Interests

My research has focused on emergency care outcomes, including cardiac arrest, emergency department revisits, triage, and the use of big data and artificial intelligence to predict rare but clinically important events. To date, I have published more than 120 peer-reviewed articles, served as the deputy director of the NTUH Integrated Medical Data Center and Center for AI Impact Evaluation, and led dozens of government-funded projects in emergency medicine and AI-based clinical prediction. My online research profile can be found at Google Scholar (https://scholar.google.com/citations?hl=en&user=PPfle3kAAAAJ) or NTU Scholars (https://scholars.lib.ntu.edu.tw/entities/person/239331c5-251a-4b4b-b83e-f202f4ef806b). My

research team's mission and work can also be found at www.em-research.net.

Major Honors and Awards

2006, 2013	Outstanding Reviewer, Annals of Internal Medicine
2006-2008	Taiwanese Physician Award, Harvard School of Public Health
2010	Partners in Excellence Award, Partners HealthCare System, MA
2022	Editor's Pick and SAEM Podcast: Physician gestalt for emergency department triage
2023	Excellent Attending Physician, NTUH

Old Problems, New Solutions: How AI is Changing Today's ER

Chu-Lin Tsai
蔡居霖

Department of Emergency Medicine, National Taiwan University Hospital and
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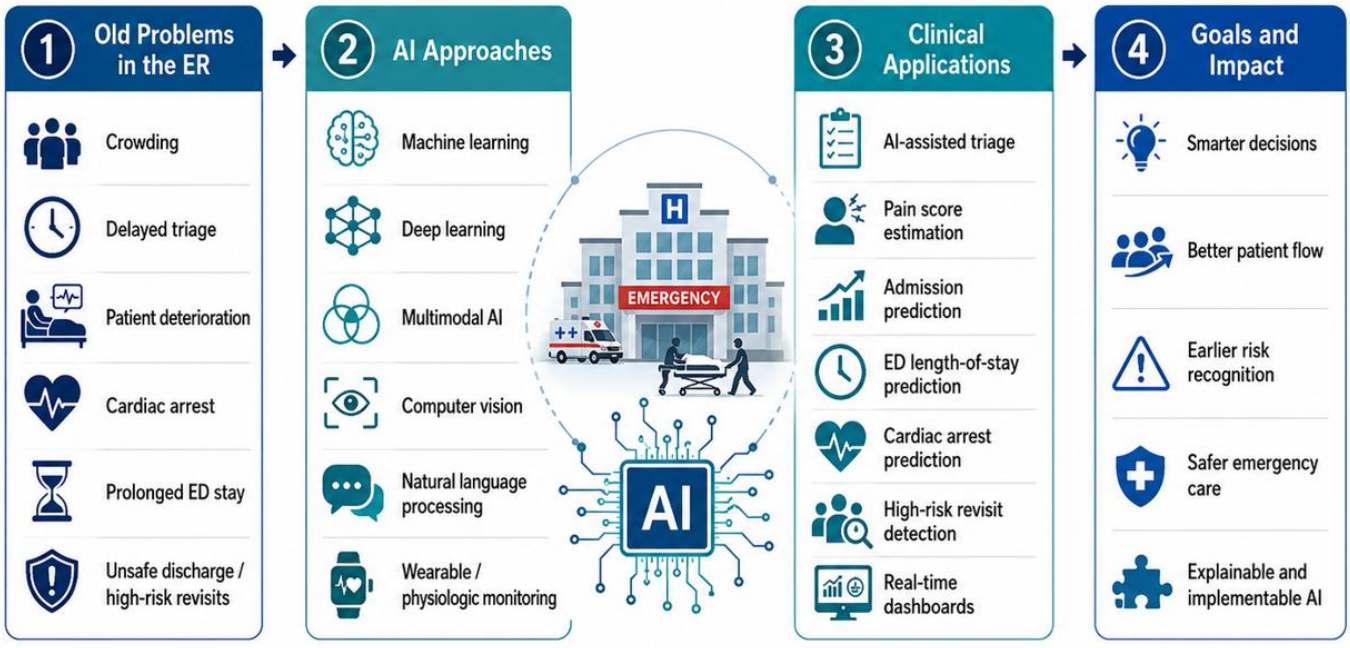
Emergency departments (aka. Emergency Rooms, [ERs]) have long faced persistent challenges: crowding, delayed triage, unpredictable patient deterioration, cardiac arrest, prolonged length of stay, and unsafe discharge. These are not new problems, but recent advances in artificial intelligence offer new opportunities to address them. In this talk, I will present how data science, machine learning, deep learning, and multimodal AI can be applied to improve decision-making across the emergency care continuum.

Key examples include AI-assisted triage, pain score estimation, prediction of hospital admission and emergency department length of stay, in-hospital cardiac arrest prediction, and identification of patients at risk for high-risk emergency department revisits.

The presentation will also highlight prospective studies using unconventional and multimodal data sources, including video, speech, chief complaint text, facial images, physiologic signals, and wearable monitoring. These approaches reflect the reality of emergency medicine, where clinicians naturally integrate multiple forms of information when assessing patients under time pressure.

A major example is the "Smart Emergency Department Capstone Project", conducted in collaboration with the NTU AI Center. This initiative integrated hospital information systems, private-cloud computing, clinical user interfaces, and real-time AI prediction models to support emergency department workflows. A subsequent example is the Center for AI Impact Evaluation, recently established to apply clinical trial design for the rigorous evaluation of AI in healthcare.

By applying new AI solutions to long-standing emergency department problems, our research aims to make today's ER smarter, safer, and more responsive to the needs of patients and clinicians.



**The above infographic was initially generated with AI assistance, manually revised.*

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Education

1998–2002	Bachelor, Department of Public Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan
2004–2006	M.S., Department of Healthcare Administration, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan
2008–2013	Ph.D, Graduate Institute of Occupational Safety and Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan

Research and Professional Positions Held in Chronological Sequence

2013–2014	Postdoctoral Fellow, Instrument Technology Research Center, National Applied Research Laboratories, Taiwan
2013–2015	Adjunct Lecturer, Faculty of Renal Care, Kaohsiung Medical University, Taiwan
2014–2018	Assistant Research Fellow, Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, Taiwan
2015–2017	Adjunct Assistant Professor, Department of Public Health, Kaohsiung Medical University, Taiwan
2015–2019	Adjunct Assistant Professor, Faculty of Renal Care, Kaohsiung Medical University, Taiwan
2018–2019	Project Assistant Professor, Master of Public Health Degree Program, College of Public Health, National Taiwan University, Taiwan
2019–2023	Assistant Research Fellow, Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan
2020–2021	Adjunct Assistant Professor, School of Nursing, Fooyin University, Taiwan
2020–present	Deputy Director, Information and Taiwan Renal Data System Committee, Taiwan Society of Nephrology
2023–present	Associate Research Fellow, Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan

Research Interests

Modeling in chronic kidney disease; national kidney disease surveillance and health policy; causal inference and advanced epidemiologic methods; health decision support and precision public health.

Major Honors and Awards

2017	Excellent Oral Presentation Award, 2nd Global Chinese Nephrology Conference and 2017 Annual Meeting of the Taiwan Society of Nephrology
2018	Excellent Oral Presentation Award, Annual Meeting of the Taiwan Society of Nephrology
2019	First Place Prize of Poster Presentation, Society for Design & Process Science

Advancing Taiwan Kidney Care: Learning from Real-World Evidence

Ming-Yen Lin
林明彥

Division of Nephrology, Kaohsiung Medical University Hospital, Taiwan

Kidney disease in Taiwan substantially shortens life expectancy and imposes considerable physical, psychological, and financial burdens on patients, caregivers, and the healthcare system. To address the growing burden of chronic kidney disease (CKD), nationwide pay-for-performance care programs were launched in the mid-2000s and early 2010s to provide more comprehensive, multidisciplinary care for patients with CKD. Previous studies have demonstrated that these programs are associated with reduced risks of end-stage kidney disease, mortality, and other adverse clinical outcomes. In addition, accumulating evidence suggests that the care programs may reduce long-term healthcare expenditures and alleviate the financial burden on the government healthcare system. Despite these promising findings, the overall coverage and referral rates for CKD care programs remain suboptimal, partly due to limited evidence supporting efficient, targeted referral policies for patients at different CKD stages.

To address this gap, the research team assembled and integrated experts from multiple disciplines to develop a comprehensive simulation framework for evaluating CKD care strategies. Using large-scale nationwide databases, we quantified gains in average life expectancy by comparing patients enrolled in CKD care programs with those identified through screening programs alone. The model further characterized transitional patterns across CKD staging and estimated stage-specific life expectancy gains to determine priority populations for care enrollment and referral. By identifying patients most likely to benefit from early multidisciplinary intervention, the framework provides evidence to support more efficient, precision-oriented CKD care policies.

In addition, the simulation model incorporated utility and healthcare cost information derived from approximately 500 participants recruited from two hospitals. Based on these data, we developed and evaluated three potential policy scenarios and conducted cost-effectiveness analyses to estimate the incremental costs per quality-adjusted life year gained under each policy setting. These analyses provide important evidence for policymakers regarding the economic value and sustainability of different CKD care strategies.

Furthermore, by leveraging data from nationwide databases and clinical cohorts, we developed interactive visualization and decision-support platforms to enhance CKD care delivery. These platforms can assist clinicians in predicting ESKD risk, facilitate personalized risk communication, and support patients in improving self-care behaviors and disease management. Collectively, this work aims to advance precision public health strategies for CKD prevention and management in Taiwan.

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Education

1979 - 1986	M.D., School of Medicine, National Yang-Ming University, Taiwan
1990 - 1992	M.P.H., College of Public Health, National Taiwan University, Taiwan
1996 - 2000	Dr.P.H., School of Public Health, Tulane University, U.S.A.

Research and Professional Positions Held in Chronological Sequence

2000 - 2001	Post-Doctoral Research Fellow, Department of Community Health Sciences, School of Public Health and Tropical Medicine, Tulane University, U.S.A.
2001 - 2006	Assistant Investigator, Division of Health Policy Research, National Health Research Institutes, Taiwan
2006 - 2014	Associate Investigator, Institute of Population Health Sciences, National Health Research Institutes, Taiwan
2012- 2014	Director, Division of Geriatrics and Gerontology, Institute of Population Health Sciences, National Health Research Institutes, Taiwan
2019-2022	Executive Director, NHRI Forum, National Health Research Institutes
2014-2026	Investigator and Deputy Director, Institute of Population Health Sciences, National Health Research Institutes
2015-present	Adjunct Professor, Institute of Clinical Medicine, National Yang-Ming University
2015-present	Joint-Appointed Professor, Department of Health Services Administration, China Medical University, Taichung
2021-present	Executive Director, National Center for Geriatrics and Welfare Research, National Health Research Institutes
2026- present	Investigator and Director, National Center for Geriatrics and Welfare Research, National Health Research Institutes

Research Interests

1. Geriatrics Research
2. Epidemiology and Care of Diabetes Mellitus
3. Epidemiology and Prevention of Chronic Kidney Diseases
4. Program Evaluation

Challenges of Youth-onset Diabetes in Taiwan

Chih-Cheng Hsu
許志成

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

Youth-onset type 2 diabetes mellitus (T2DM) is emerging as a critical public health challenge in Taiwan, diverging from the stabilizing trends observed in older populations. Using nationwide insurance and registry data, this presentation highlights the epidemiological burden, clinical trajectories, and outcome disparities associated with early-onset T2DM. In 2021, T2DM accounted for over 99% of the 2.66 million diabetes cases in Taiwan, with an incidence of 0.83% and mortality of 2.9%. While overall incidence rates have declined in high-risk groups aged ≥40 years, prevalence among individuals aged 20-39 years has risen steadily, with a 21.5% increase over five years. This younger cohort, though comprising only about 3% of total cases, demonstrates disproportionate disease progression.

Life expectancy analyses reveal persistent gaps of 3-6 years compared with the national average, most pronounced in younger adults. Cardiovascular outcomes show encouraging macro trends, with reductions in major adverse cardiovascular events (MACE), stroke, and cardiovascular deaths between 2017 and 2021. However, subgroup analyses underscore a paradox: despite systemic improvements, youth-onset T2DM patients face significantly elevated hazards of ischemic heart disease, heart failure, stroke, and composite cardiovascular disease compared with type 1 diabetes peers. Fully adjusted hazard ratios for cardiovascular outcomes in T2DM onset <25 years ranged from 1.47 to 1.86, while those for onset at 25-39 years reached 1.51-1.98. All-cause and cardiovascular mortality risks were also markedly higher, with the 25-39 cohort exhibiting a threefold increase in cardiovascular death relative to childhood-onset T1D.

Youth-onset T2DM in Taiwan represents a high-risk epidemic characterized by rapid therapeutic failure, severe premature cardiorenal complications, and extensive undetected prevalence driven by shifting obesogenic lifestyle patterns. Managing this crisis demands a paradigm shift away from conservative "watch and wait" regimens toward early, aggressive renoprotection, tailored lifetime risk modeling, and dedicated youth-specific clinical care pathways.

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-EX115-11029SI
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: 3 years)

Background: Epigenetic dysregulation and gut microbiota dysbiosis are correlated with osteoporosis development. Epigenetic histone lysine and arginine demethylases play a critical role in erasing repressive transcription, thereby maintaining tissue metabolism and microenvironment homeostasis. The impact of gut beneficial microorganisms on histone demethylase-dependent osteogenic capacity and bone mass homeostasis remains unexplored.

Objectives: Using osteoblast-specific conditional H3K27me3 demethylase *Utx* knockout mice (UtxKO), conditional histone arginine demethylase *Jmjd7* knockout mice (Jmjd7KO mice) and germ-free (GF) mice, we investigate the effect of gut beneficial microorganism transplantation on osteogenic and osteoclastogenic differentiation capacity and bone microarchitecture. We also elucidate the molecular mechanism underlying methyl-acetyl shift in H3K27 in *Utx*KO osteoblasts.

Materials and Methods: Key parameters of bone microstructure, including bone mineral density, trabecular/cortical bone networks were investigated using micro-CT imaging. Viable and heat-inactivated gut microorganisms were transplanted into *Utx*KO mice and GF mice. Osteogenic capacity of bone-marrow mesenchymal progenitor cells was investigated using von Kossa stain. Transcriptome and gut microbiome were elucidated using RNA-seq and 16S RNA-seq. Methyl and acetylate histone-enriched epigenomic landscapes were characterized using CUT&Run sequencing.

Results: Utx deletion leads to impaired osteogenesis, severe osteoporosis alongside gut microbiota dysbiosis, particularly the decreased abundance of gut beneficial microorganisms. Specifically, gut beneficial bacteria-transplanted *Utx*KO mice demonstrate mitigated osteoporosis features, including low bone mass, sparse trabecular microstructure, and decreased bone biomechanical strength. Gut beneficial microorganism transplantation rebalances gut microenvironment integrity, immune response and gut microbiota profiles. Utx loss rewires acetylated lysine, methylated lysine and arginine histone patterns alongside decreased Jmjd5, Jmjd6, and Jmjd7 expression in osteogenic cells. Importantly, *Jmjd7*KO mice exhibit delayed cranial suture closure, kyphosis, and severe osteoporosis through repressing mitochondrial OXPHOS. Mechanistically, Utx loss aggravates acetyl-methyl shift in H3K27 by impairing Sirt1, thereby activating the interaction between histone methyltransferase Eed (a PRC2 member) and acetylation reader Brd4. Inhibition of Brd4 promotes acetyl H3K27-enriched epigenome that mitigates Utx deletion-induced osteogenesis loss, corroborating that osteoblast specific *Brd*4-*Utx*KO double knockout mice demonstrate attenuated osteoporosis.

Conclusions: Our comprehensive analyses convey new insight into gut-bone axis and highlight the bone-anabolic effect of gut beneficial bacteria on skeletal disorders. These investigations also shed light on the crosstalk between histone demethylases and an acetylation reader that recognizes the Utx loss-induced acetyl-methyl shift in H3K27, opening a new avenue to develop epigenetic remedy option against osteoporosis.

Title of Project: Targeting the Ketogenesis Pathway for Tissue Rejuvenation
Project No.: NHRI-EX115-11203SI
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 knockout HMGCS2 in cardiomyocytes (CM-HMGCS2$^{-/-}$). This genetic manipulation resulted in a progeroid phenotype characterized by reduced lifespan and impaired cardiac function in an age-dependent manner. Additionally, mitochondrial function assessed through Seahorse and ^{13}C-labeled metabolite consumption analysis showed a reduced oxygen consumption capability in CM-HMGCS2$^{-/-}$ mice. Mechanically, we found that HMGCS2 deficiency leads to a decline in βOHB-dependent β-hydroxybutyrylation (Kbhb). To identify the targets of Kbhb controlled by cardiac ketogenesis, we performed anti-Kbhb affinity enrichment followed by LC-MS proteomics. This analysis identified 91 Kbhb-modified proteins lacked detectable modification upon HMGCS2 deficiency. Intersecting this proteome with a published dataset of aging-downregulated cardiac Kbhb proteins revealed three shared key targets that undergo reduced Kbhb modification in both conditions: dihydrolipoamide dehydrogenase, dihydrolipoamide S-succinyltransferase, and ATP synthase subunit 8.

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: Study the Physiological Function of the Miltenberger Blood Group Antigen Type III (GP.Mur) and Explore Its Gene Evolution in Taiwan.
Project No.: NHRI-EX115-11313SI
P.I.: Yei-Tsung Chen/陳儀聰
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Humanized Zebrafish Reveal a Novel Role of Human Glycophorins in Energy Homeostasis and Cardiovascular Function

Ferry Saputra, Tran Thi Tu Trang, Nguyen Ngoc Diep, Tran Ngan Tra, and Yei-Tsung Chen
Department of Life Sciences and Institute of Genome Sciences,
National Yang Ming Chiao Tung University

The Miltenberger (Mi) blood group system comprises red blood cell antigens generated by homologous recombination between GYPA and GYPB. Among these hybrid GPs, glycophorin Mur (GP.Mur; Mi.III), encoded by the GYPB-A-B hybrid gene, is highly prevalent in Southeast Asian populations, occurring in approximately 4.5% of Taiwanese individuals and at even higher frequencies among indigenous groups. While glycophorins are recognized as structural components of erythrocyte membranes, emerging evidence suggests that GP.Mur carriers exhibit superior physical endurance, indicating previously unrecognized physiological functions of GPs.

To investigate the *in vivo* roles of human glycophorins, we established humanized zebrafish that express either human GYPA (Tg(hGYPA)) or the GP.Mur hybrid glycophorin GYPB-A-B (Tg(hGYPBAB)). Zebrafish is an ideal vertebrate model because it has only a GYPC ortholog, allowing evaluation of human glycophorin function without interference from endogenous GYPA/GYPB homologs. Results from the current study show that both transgenic lines exhibited normal morphology and development throughout embryonic and larval stages. Functional analyses, however, revealed significantly enhanced cardiac performance, with increased ejection fraction and cardiac output in both Tg(hGYPA) and Tg(hGYPBAB) larvae. Remarkably, Tg(hGYPBAB) larvae displayed lower oxygen consumption despite greater spontaneous locomotor activity and elevated ATP levels, suggesting improved metabolic efficiency. Consistent with these observations, expression of the energy stress-associated genes aprt and prkaa1 was reduced in both transgenic lines relative to wild-type controls, indicating the absence of cellular energy deprivation. Moreover, HPLC analyses showed no differences in lactate or acetate concentrations, suggesting that enhanced ATP availability was not driven by increased glycolysis or anaerobic metabolism. Instead, these findings support improved energy production and/or ATP utilization efficiency.

In summary, we generated the first humanized zebrafish models expressing human glycophorins and demonstrated that these proteins regulate whole-organism energy homeostasis and cardiovascular performance. Our findings uncover previously unknown physiological functions of human glycophorins beyond their roles in erythrocyte membrane structure and provide a mechanistic explanation for the enhanced physical performance associated with the GP.Mur blood type.

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

Project No.: NHRI-EX115-11314SI
P.I.: Yu Feng Hu/胡瑜峰
Key Professional Personnel: Pei-Chun Chou/周姵君, Ching-Hui Wong/翁靖惠, Mu-Jou Tseng/曾慕柔, Chih-Min Liu/劉至民
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Sinoatrial node dysfunction (SND) is the leading cause of pathological bradycardia, manifesting as weakness, syncope, and cardiac arrest. Current therapy relies exclusively on electronic pacemaker implantation, which corrects slow heart rhythm without addressing the underlying disease mechanism. We previously identified aldolase C (ALDOC), a glycolytic enzyme, as a key regulator of sinoatrial node (SAN)-specific aerobic glycolysis and electrical rhythmicity. Building on this discovery, this integrated project investigated whether age-related ALDOC deficiency and impaired glycolysis represent causal and therapeutically targetable mechanisms of SND.

Naturally aged mice recapitulated the human SND phenotype, exhibiting slower heart rates and frequent prolonged sinus pauses. Quantitative proteomic analysis of young and aged SAN tissues demonstrated downregulation of ALDOC and multiple glycolytic enzymes, accompanied by enrichment of inflammatory neutrophil-degranulation pathways. Pharmacological inhibition of glycolysis with 2-deoxy-D-glucose acutely reduced heart rate, directly supporting a role for glycolytic flux in SAN pacemaking. Aldoc-knockout zebrafish further exhibited impaired exercise capacity, suggesting functional consequences of ALDOC deficiency across vertebrate models.

To establish causality in mammals, we generated a cardiac-specific, tamoxifen-inducible conditional ALDOC-knockout mouse (MerCreMer/loxP). Control experiments confirmed that the Cre/loxP system itself introduced no growth, morphological, or gene-expression confounders. Conditional ALDOC deletion markedly reduced SAN ALDOC expression and prolonged maximal sinus pauses while preserving baseline heart rate and autonomic responses to isoproterenol and methacholine, indicating selective impairment of intrinsic pacemaker stability rather than autonomic regulation. Consistent with these findings, aged SAN tissues displayed reduced ALDOC expression, prolonged sinus pauses, and increased CD45-positive immune-cell infiltration.

Finally, systemic administration of recombinant ALDOC protein successfully reached the SAN in aged mice, significantly reduced maximal sinus pause duration and beat-to-beat pause variability, and attenuated SAN inflammatory cell infiltration without affecting baseline heart rate. Collectively, these complementary loss- and gain-of-function studies identify ALDOC-dependent aerobic glycolysis as a fundamental metabolic regulator of SAN rhythmic stability. Our findings demonstrate that age-related ALDOC deficiency contributes directly to SND and that restoration of ALDOC represents a promising SAN-targeted metabolic strategy for treating chronotropic incompetence and reducing reliance on electronic pacing.

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-EX115-11315SI
P.I.: Wei-Chieh Cheng/鄭偉杰
Key Professional Personnel: Shu-Chen Kuo/郭書辰, Chun-Kai Wang/王鈞楷, Po-Yi Hsu/許博宜, Shih-Chen Ho/何師辰
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

The rapid emergence of antimicrobial resistance has created an urgent need for antibiotics with new mechanisms of action. Uridine-containing natural products (nucleoside antibiotics) represent one of the most promising classes of antibacterial agents because they target MraY (phospho-*N*-acetylmuramoyl-pentapeptide transferase), an essential membrane enzyme that catalyzes the first committed step of bacterial peptidoglycan biosynthesis. By mimicking natural UDP-sugar substrates, these molecules exhibit potent antibacterial activity against a broad spectrum of clinically important pathogens. Despite their exceptional biological activities, the therapeutic potential of naturally occurring nucleoside antibiotics—including mureidomycins, pacidamycins, napsamycins, sansanmycins, and tunicamycins—has remained largely unrealized. Their highly complex molecular architectures, numerous stereogenic centers, and extremely limited natural abundance present formidable challenges for chemical synthesis, structure-activity relationship (SAR) studies, medicinal chemistry optimization, and large-scale production. Consequently, the development of structurally simplified MraY inhibitors that retain potent antibacterial activity has become a major objective in antibiotic discovery. To address this challenge, we developed a **natural product-inspired combinatorial chemistry (NPICC)** platform to systematically redesign the uridine antibiotic scaffold. Rather than reproducing complex natural products, our strategy captures their essential pharmacophore while introducing modular diversification through scaffold, stereochemical, and substituent variations. This design enables the rapid generation of structurally accessible analogues with substantially reduced synthetic complexity while preserving the key molecular features required for MraY inhibition. Systematic biological evaluation of this focused library identified several promising MraY inhibitors, including compounds **19, 33, 34, and 35**, which demonstrated both potent enzymatic inhibition and antibacterial activity. Importantly, these lead compounds also exhibited therapeutic efficacy in the ***Galleria mellonella*** infection model, with compound **34** showing the most favorable *in vivo* performance, thereby validating the effectiveness of our simplified molecular design.

Building upon these encouraging results, our current efforts focus on combination therapy by pairing our MraY inhibitors with clinically used antibiotics and functional adjuvants to enhance antibacterial potency, overcome bacterial tolerance, and suppress the emergence of resistance. Collectively, this work establishes NPICC as a powerful platform for transforming structurally complex natural products into synthetically accessible antibacterial leads and provides a promising strategy for the development of next-generation antibiotics targeting bacterial cell wall biosynthesis.

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-EX115-11316SC
P.I.: Yu-Hsiang Chou/周鈺翔
Key Professional Personnel: Yu-Han Shao/邵鈺涵
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Background

Acute kidney injury (AKI) is a major clinical condition associated with high morbidity and an increased risk of progression to chronic kidney disease (CKD). Emerging evidence suggests that metabolic reprogramming following AKI plays a critical role in renal repair and the transition from AKI to CKD. We previously demonstrated that pretreatment with tamoxifen (TAM) attenuates ischemia-reperfusion injury (IRI)-induced AKI. Building on these findings, we hypothesized that TAM promotes renal recovery after IRI-AKI by modulating amino acid and lipid metabolism.

Methods

To investigate the effects of TAM on AKI, we used *Pax8-rtTA;LC-1;tdTomato* mice to isolate renal tubular cells following IRI. These cells were subjected to analyses of amino acid and fatty acid transporters, as well as metabolism-related gene expression. To characterize TAM-induced metabolic alterations, amino acid levels in plasma, kidney tissue, and urine were quantified using a custom-developed liquid chromatography–mass spectrometry (LC-MS) platform.

Based on our previous findings that TAM pretreatment upregulated *Slc7a12* and *Ugt1a2* expression, we generated *Slc7a12* knockout mice and *Ugt1a2* knockout mice respectively using CRISPR/Cas9 technology and crossed them with *Pax8-rtTA;LC-1* mice to generate *Pax8-rtTA;LC-1;Slc7a12*$^{F/F}$ mice and *Pax8-rtTA;LC-1; Ugt1a2*$^{F/F}$, enabling investigation of the role of Slc7a12 and Ugt1a2 in the renoprotective effects of TAM.

Results

We found that the expression of the amino acid transporters *Slc7a12* and *Slc3a2*, as well as the lipid glucuronidation enzyme *Ugt1a2*, was significantly upregulated in TAM-treated mice compared with controls, consistent with our previous RNA-sequencing results. We also successfully generated *Pax8-rtTA;LC-1;Slc7a12*$^{F/F}$ mice, which developed normally without an overt phenotype.

TAM pretreatment increased plasma leucine levels while decreasing urinary leucine levels following IRI-induced AKI, suggesting reduced urinary leucine loss and enhanced renal conservation of leucine.

In vitro, TGF-β1 stimulation reduced the expression of the mitochondrial transporter *Slc25a12* in 3T3 fibroblasts, suggesting a potential role for Slc25a12 in regulating pericyte metabolism following injury.

Conclusions

Alterations in amino acid and lipid metabolism play a critical role in renal recovery following IRI-induced AKI. The upregulation of the amino acid transporter Slc7a12 and the lipid metabolism-related protein Ugt1a2 in renal tubular cells underlie the renoprotective effects of TAM pretreatment. We successfully generated Pax8-rtTA;LC-1;*Slc7a12* $^{F/F}$ mice, which provide a valuable model for investigating the renoprotective mechanisms of TAM. In addition, our findings highlight a potential role for the mitochondrial transporter Slc25a12 in regulating pericyte metabolism during renal repair after AKI.

Title of Project: The Functional Role of a Novel E3 Ubiquitin Ligase in the Regulation of Necroptosis
Project No.: NHRI-EX115-11334SI
P.I.: Li-Chung Hsu/徐立中
Key Professional Personnel: Tzu-Yu Pu/蒲姿佑, Hsien-Ping Chiu/邱顯平, Yuan-Sin Wang/王遠馨, 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 that is triggered by activation of pattern recognition receptors (PRRs) or death receptors (DRs). Upon stimulation, receptor-interacting serine/threonine-protein kinase 3 (RIPK3) is activated and subsequently phosphorylates mixed lineage kinase domain-like pseudokinase (MLKL), ultimately inducing necrotic cell death. Necroptosis has been implicated in numerous physiological processes, including host defense against pathogens and tumors, tissue regeneration, and embryonic development. However, dysregulated necroptosis contributes to excessive inflammation and the pathogenesis of various inflammatory diseases. Our laboratory previously identified a novel E3 ubiquitin ligase as an important regulator of Toll-like receptor (TLR)-mediated immune responses by ubiquitinating distinct signaling proteins to modulate multiple innate immune pathways. To further investigate its biological functions, we performed unbiased ubiquitylome and proteome analyses, which identified RIPK3 as a previously unrecognized interacting partner of this E3 ubiquitin ligase, suggesting its potential role in the regulation of necroptosis. In this study, we demonstrate that deletion of this E3 ubiquitin ligase in murine macrophages markedly suppresses necroptotic cell death and reduces RIPK3 and MLKL phosphorylation following poly(I:C) or LPS stimulation in the presence of the pan-caspase inhibitor zVAD, indicating that this E3 ubiquitin ligase positively regulates TRIF-dependent necroptosis. Mechanistically, we show that RIPK3 interacts with the E3 ubiquitin ligase through both its kinase domain and RIP homotypic interaction motif (RHIM). Importantly, the E3 ligase activity is required for efficient necrosome assembly and subsequent activation of RIPK3-dependent necroptotic signaling. Furthermore, E3 ubiquitin ligase-deficient mouse embryonic fibroblasts exhibit impaired RIPK3 and MLKL phosphorylation and reduced accumulation of influenza A virus (IAV) NS1 protein following viral infection. Collectively, our findings identify this novel E3 ubiquitin ligase as a positive regulator of RIPK3-mediated necroptosis. By promoting necrosome assembly through its E3 ubiquitin ligase activity, this protein facilitates necroptotic signaling and antiviral defense, providing new mechanistic insight into the ubiquitin-dependent regulation of necroptosis and highlighting a potential therapeutic target for inflammatory and viral diseases.

Title of Project: To Investigate the Mechanism of PP4 in Regulating NETs Formation During Sepsis
Project No.: NHRI-EX115-11335SI
P.I.: Feng-Ming Yang/楊豐名
Key Professional Personnel: Mei-Chun Lin/林玫君
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Sepsis is a life-threatening clinical syndrome caused by a dysregulated innate immune response to infection, resulting in excessive systemic inflammation, multiorgan failure, and persistently high mortality rates. In fatal human sepsis, phosphoprotein phosphatase 4 (PP4) expression is markedly reduced in myeloid cells, suggesting a protective role against dysregulated innate immunity. However, its role in macrophage-neutrophil crosstalk during sepsis environment remains unclear. To delineate its cell-type specificity, we generated myeloid cell-specific PP4 knockout mice and investigated PP4's function in innate immune regulation during sepsis. PP4-deficient mice exhibited significantly increased susceptibility to sepsis, with severe tissue damage following cecal ligation and puncture (CLP) or endotoxin challenge. Mechanistically, PP4 modulates macrophage-neutrophil crosstalk during the sepsis environment, with its loss leading to dysregulated CCL5/CCR5 signaling, driving excessive neutrophil activation. Elevated macrophage-derived CCL5 enhanced PAD4-dependent NETosis, ROS production, and elastase activity via CCR5, while CCR5 inhibition effectively mitigated neutrophil hyperactivity. At the molecular level, PP4 directly dephosphorylated TBK1, thereby inactivating IRF3 and suppressing macrophage-driven CCL5 production. Furthermore, ERK1/2 phosphorylation upregulated CCR5 expression in PP4-deficient neutrophils post-CLP, amplifying the CCL5/CCR5-mediated NETosis response. Notably, transfection with wild-type PP4-but not a phosphatase-deficient mutant-reduced LPS-mediated CCR5 expression in neutrophils, thereby limiting ROS production and NETs formation. These findings establish PP4 as a critical regulator of CCL5/CCR5-driven NETosis, uncovering a novel therapeutic target for modulating innate immune responses in sepsis.

Title of Project: Investigating the Pathophysiological Mechanism of K2P Channelopathy in Maturity Onset Diabetes of the Young
Project No.: NHRI-EX115-11336SI
P.I.: Shi-Bing Yang/楊世斌
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Age-Dependent Redistribution of the TALK1-L114P Potassium Channel Underlies the Transition from Neonatal Diabetes to MODY

Gain-of-function mutations in the pancreatic two-pore domain potassium channel TALK1 (KCNK16) are a recently identified cause of maturity-onset diabetes of the young (MODY), yet the mechanisms responsible for the transition from severe neonatal diabetes to the relatively mild adult phenotype remain unclear. Using a CRISPR/Cas9-generated TALK1-L114P knock-in mouse model, we investigated the age-dependent regulation of β-cell excitability through electrophysiology, pancreatic slice calcium imaging, histological analyses, and computational modeling. Neonatal TALK1-L114P mice developed severe transient hyperglycemia associated with markedly impaired glucose-stimulated insulin secretion and increased β-cell membrane potassium conductance. Whole-cell recordings demonstrated that excessive membrane-localized TALK1-L114P activity hyperpolarized β-cells and suppressed electrical excitability during the early postnatal period. Remarkably, membrane conductance returned to near wild-type levels after postnatal day 10, coinciding with recovery of insulin secretion and normalization of blood glucose in surviving animals. Adult mutant mice subsequently exhibited only moderate glucose intolerance resembling MODY in human patients. Despite this apparent recovery, adult β-cells displayed substantial heterogeneity in membrane conductance and electrical activity. Calcium imaging further revealed heterogeneous glucose responsiveness among individual islets while preserving coordinated β-cell network activity in responsive islets. Mathematical modeling demonstrated that modest increases in background potassium conductance are sufficient to shift β-cell electrical behavior from tonic firing to bursting or electrical silence, providing a mechanistic explanation for the observed functional heterogeneity. These findings identify age-dependent redistribution of membrane-localized TALK1-L114P channels as a key determinant of disease progression from transient neonatal diabetes to adult MODY. Our study reveals ion channel trafficking as a previously unrecognized mechanism regulating β-cell excitability and glucose homeostasis and highlights potassium channel trafficking as a potential therapeutic target for monogenic diabetes.

Title of Project: TERRA-mediated Epigenetic Regulation and TERRA R-loop Induced Cytosolic Immune Response Underlie Human Aging

Project No.: NHRI-EX115-11411SI

P.I.: Hsueh-Ping Chu/朱雪萍

Affiliation/Institution: National Taiwan University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

Telomeric transcription gives rise to telomeric repeat-containing RNA (TERRA), a long noncoding RNA composed of UUAGGG repeats. We previously demonstrated that TERRA associates with the telomerase complex and plays important roles in maintaining telomere integrity, regulating epigenetic states, and modulating DNA G-quadruplex (G4) structures in mammalian cells. TERRA can also form DNA:RNA hybrids (R-loops) at telomeres, leading to activation of the DNA damage response and replication stress. However, whether and how TERRA contributes to human aging remains largely unknown.

Using long-read nanopore sequencing, we mapped the transcriptional origins of TERRA at the ends of individual human chromosomes. We recently reported that TERRA levels increase with age across multiple human tissues, including blood, brain, and fibroblasts (Nucleic Acids Research, 2025). Furthermore, single-cell RNA-sequencing analysis revealed elevated TERRA expression in neurons during the early stages of Alzheimer's disease progression.

To investigate the role of TERRA in human aging, we examined whether TERRA activates innate immune signaling during cellular senescence. We found that increased TERRA expression coincides with elevated senescence markers and upregulation of genes involved in innate immune responses. Notably, cytosolic TERRA-associated RNA:DNA hybrids accumulate in senescent cells. Depletion of TERRA attenuates the expression of IFN-α, IFN-β, and p21, indicating that TERRA contributes to the establishment of the senescent phenotype. Remarkably, neurons from Alzheimer's disease patients exhibit elevated TERRA levels accompanied by reduced expression of genes involved in mitochondrial biogenesis, including PGC-1α, NRF2 and TFAM. TERRA depletion partially restores the expression of these genes, suggesting a functional link between TERRA and mitochondrial dysfunction.

Collectively, our findings identify TERRA as a driver of innate immune activation and cellular senescence, revealing a previously unrecognized role for TERRA in human aging and age-associated neurodegenerative disease.

Title of Project: Unveiling the Molecular Biology of the Universally Conserved Coronavirus Octamer and Evaluating the Novel Targets for Antiviral Designs by Multi-omics Integration

Project No.: NHRI-EX115-11412SI
P.I.: Hung-Yi Wu/吳弘毅
Key Professional Personnel: Chun-Chun Yang/楊淳鈞
Affiliation/Institution: National Chung Hsing University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

The conserved octamer 5'GGAAGAGC3' located in the hypervariable region (HVR) of the 3' untranslated region of coronaviruses is present across all four coronavirus genera, suggesting an important but still poorly defined role in the viral life cycle. To elucidate its function with minimal prior assumptions, we combined RNA–protein interactomics with biochemical assays to interrogate octamer-dependent RNA–protein networks and viral RNA stability under defined infection conditions. Biotinylated HVR RNAs harboring either wild-type (HVR-wt) or octamer-mutant (HVR-octm) sequences were subjected to RNA–protein pull-down and LC–MS/MS using lysates from mouse L cells infected with either mouse hepatitis virus (MHV)-A59-wt or the octamer-mutant virus MHV-A59-octm under two settings: without or with IFNβ pretreatment. In parallel, liver lysates from mice infected with MHV-A59-wt or MHV-A59-octm at different days postinfection were analyzed in the same way. Gene Ontology enrichment analysis of these interactomes consistently revealed strong enrichment of translation- and protein folding-related processes in both HVR-wt and HVR-octm conditions, with octamer-dependent differences in protein folding, protein stabilization and mRNA stability-related factors. Notably, the RNA stability-associated RNA-binding proteins ELAVL1 and YBX1 were selectively identified in the HVR-wt interactome from mock-treated, MHV-A59-wt–infected cells, implicating the octamer in promoting viral RNA stability during early infection. To functionally validate this hypothesis, we constructed coronavirus defective viral genomes (DVGs) and multi-ORF minigenomes carrying either wild-type (DVG-wt/MG-wt) or octamer-mutant (DVG-octm/MG-octm) sequences and quantified RNA decay kinetics in HEK-293T cells under mock infection, infection, and infection-mimicking conditions. RT-PCR and RT-qPCR analyses demonstrated that DVG-wt and MG-wt RNAs were consistently more stable than their octamer-mutant counterparts, and that this stability advantage extended to subgenomic mRNAs derived from MG-wt. Furthermore, overexpression of the zinc-finger antiviral protein ZAP, which targets CpG-rich viral RNA for degradation, selectively reduced the levels of octamer-mutant RNAs, indicating that the conserved octamer counteracts ZAP-mediated viral RNA decay. Together, our data support a model in which the universal coronavirus octamer shapes an RNA–protein interactome enriched in translation and folding factors while simultaneously stabilizing genomic and subgenomic RNAs against host antiviral RNA-degradation pathways. These findings identify the octamer-centered RNA stability and protein folding axis, as well as its associated host factors, including ZAP, ELAVL1 and YBX1, as potential targets for future antiviral strategy development.

Title of Project: Developing Excipient-Free Inhalable Powders of Bedaquiline and Pyrazinamide Using Spray Drying for Potential Treatment of Tuberculosis

Project No.: NHRI-EX115-11423SC
P.I.: Wei-Ren Ke/柯威任
Key Professional Personnel: Hsiao-Chi Chuang/莊校奇, Yu-Chun Lin/林育君, Philip Chi Lip Kwok, Dipesh Khanal
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Tuberculosis (TB), particularly multidrug-resistant TB (MDR-TB), remains a major global health challenge due to the limitations of conventional oral therapy. Bedaquiline (BDQ) is an effective diarylquinoline for MDR-TB treatment, but its high cost limits accessibility in TB-endemic regions. Previous studies have shown strong synergy between BDQ and pyrazinamide (PZA), which may accelerate bacterial clearance and improve treatment outcomes. Pulmonary delivery offers a promising strategy by depositing drugs directly in the lungs, potentially enhancing local efficacy while reducing systemic toxicity. This study aimed to develop an excipient-free inhalable dry powder containing BDQ and PZA using three-fluid nozzle spray drying, with a focus on producing composite particles suitable for efficient aerosol delivery and cost-effective manufacturing.

A Box-Behnken experimental design was applied to optimize the formulation, focusing primarily on production yield. The investigated parameters included inlet temperature, BDQ-to-PZA feeding rate ratio, and PZA concentration. The optimized powder was characterized for hygroscopicity, morphology, thermal behavior, crystallinity, particle size distribution, and drug content uniformity using dynamic vapor sorption (DVS), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and laser diffraction. *In vitro* aerosol performance was evaluated by loading 10 mg of powder into size-3 capsules and dispersing the formulation through the Sunriser device into a Next-Generation Impactor.

The optimized spray-drying condition achieved a maximum powder yield of 67.43% at an inlet temperature of 77°C, BDQ-to-PZA feeding rate ratio of 3.2, and PZA concentration of 4.9 mg/mL. Statistical analysis indicated that yield was positively associated with PZA concentration and inlet temperature, while the feeding rate ratio showed a negative effect. SEM images showed spherical particles with wrinkled surfaces. XRD and DSC analyses confirmed a partially crystalline formulation composed of crystalline PZA and amorphous BDQ, with recrystallization observed at 136°C followed by decomposition at 149°C. The powder showed low moisture uptake of 1.34% at 25°C/80% RH, indicating slight hygroscopicity. The particle size distribution showed a D50 of 1.75 ± 0.02 μm, with D10 and D90 values of 0.80 ± 0.02 μm and 4.51 ± 0.30 μm, respectively. Content uniformity was acceptable, with PZA and BDQ recoveries of 99.03% and 107.99%, although the final PZA-to-BDQ mass ratio was 4.50:1, slightly below the target ratio of 5:1. Aerodynamic assessment demonstrated favorable inhalation performance, with MMAD values of 3.03 ± 0.02 μm for PZA and 2.55 ± 0.02 μm for BDQ. The fine particle fractions were 79.8 ± 0.2% and 88.1 ± 0.5%, respectively.

Overall, this study demonstrates the feasibility of an excipient-free PZA-BDQ inhalable dry powder prepared by three-fluid nozzle spray drying. The optimized formulation showed good yield, low hygroscopicity, suitable particle size, acceptable drug uniformity, and strong aerosol performance, supporting its potential as a targeted pulmonary therapy for TB.

Title of Project: Blockage of Folate Metabolism Maintains Diploidy in Adult Cardiomyocyte for Heart Regeneration

Project No.: NHRI-EX115-11424SC
P.I.: Yuanyuan Cheng/鄭媛元
Key Professional Personnel: Ting Hsieh/謝葶
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Heart disease is always the leading cause of death worldwide, and the heart replacement is considered to be the only treatment for heart failure until now. Poor cardiac regeneration is due to the loss of proliferative ability in adult cardiomyocyte after birth, so the remnant cardiomyocytes cannot compensate the death in the infarct area after injury. After birth or after heart injury, DNA polyploidy in adult cardiomyocytes is essential for maintain their differentiation and survival when encountering high oxygen stress. According to those species containing complete regenerative ability, the cardiomyocytes maintain diploidy which can be easily induced proliferation for full recovery of heart function after injury. Therefore, DNA polyploidy is thought to be the hurdle for mammalian heart regeneration. In our previous study, gene expressions in nucleotide metabolism were downregulated in reprogramming cardiomyocytes after induction of Yamanaka's OSKM expression for 2 days by microarray analysis. In this functional grouping, FOLR2 is the receptor to receive folate to initiate one carbon metabolism for nucleotide synthesis, and its expression was examined significantly downregulated in the reprogramming cardiomyocytes after OSKM induction. In our preliminary data, folate was confirmed to increase DNA polyploidy in rat cardiac H9C2 cells dose-dependently. Therefore, we hypothesize that FOLR2 may block folate metabolism to decrease DNA polyploidy in adult cardiomyocytes for supporting heart regeneration after injury. Based on this hypothesis, we propose to confirm the role of FOLR2 in heart development and heart regeneration after injury through blocking folate metabolism and to generate the specific antibody for targeting FOLR2 as the therapeutic drug for treatment of heart diseases. For current progress, we have confirmed that combined folate supplementation with Yamanaka's 4 factor expression in reprogramming hearts significantly increased FOLR2 expression and enhanced multi-nuclei in the adult cardiomyocytes. Oppositely, folate agonist methotrexate supplementation decreased the phenomena of multi-nuclei in the adult cardiomyocytes. In addition, the decreasing level of glycosylated FOLR2 expression was higher than the native FOLR2 protein expression in the adult cardiomyocyte after inducing reprogramming. Besides, only glycosylated FOLR2 protein expression was also detected higher in the hearts 48 hours after ischemic reperfusion. Therefore, glycosylation of FOLR2 proteins implies an essential role in heart regeneration. Therefore, we would like to measure FOLR2 glycosylation in the reprogramming hearts by LC-MS/MS and plan to produce the antibody specifically for glycosylated FOLR2 for supporting heart regeneration after injury.

Title of Project: Utilizing Artificial Intelligence to Optimize Chest Compression Region During Cardiopulmonary Resuscitation for Patients with Outof- Hospital Cardiac Arrest (AIR-CPR)

Project No.: NHRI-EX115-11434SI
P.I.: Sheng-En Chu/朱聖恩
Key Professional Personnel: Sheng-En Chu/朱聖恩, Chun-Hsiang Chan/詹竣翔, Jen-Tang Sun/孫仁堂, Chieh-Min Fan/范傑閔, Matthew Huei-Ming Ma/馬惠明, Wen-Chu Chiang/江文苖
Affiliation/Institution: Far Eastern Memorial Hospital
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Introduction- Aortic valve (AV) compression during cardiopulmonary resuscitation (CPR) may obstruct left ventricular outflow and reduce forward blood flow. Although transesophageal echocardiography (TEE) can directly identify AV compression, its routine implementation is limited by equipment availability and operator requirements. This study evaluated whether AV compression could be recognized from arterial blood pressure (ABP) waveform morphology using a machine-learning model.

Methods- This prospective observational study enrolled adult patients with non-traumatic out-of-hospital cardiac arrest who underwent CPR in the emergency department with simultaneous femoral ABP monitoring and TEE. Individual compression-generated ABP waveforms were automatically segmented using a matched-filtering algorithm. Two emergency physicians classified each waveform as AV compression or no AV compression according to synchronized TEE images. Each waveform was fitted using a three-component Gaussian mixture model, from which 15 morphological features were extracted. The dataset was randomly divided into training and testing sets at a 7:3 ratio. An extreme gradient boosting model was developed using grid-search hyperparameter optimization and 10-fold cross-validation. Shapley additive explanations were applied to evaluate feature importance.

Results- Thirty patients were included, providing 28,029 synchronized, labeled, and feature-encoded ABP waveforms. In the training set, the model achieved a precision of 0.9289, recall of 0.8196, F1-score of 0.8708, and accuracy of 0.9123. In the testing set, the corresponding values were 0.9053, 0.8017, 0.8503, and 0.8992. The most influential predictors were the base width of the first Gaussian component, the peak height of the third Gaussian component, and the peak height of the second Gaussian component.

Conclusion- Machine-learning analysis of arterial pressure waveform morphology demonstrated good performance in identifying AV compression during CPR. This approach may provide a practical real-time method for recognizing unfavorable compression mechanics and supporting individualized chest-compression positioning when continuous TEE assessment is unavailable.

Title of Project: Deciphering the Molecular Crosstalk Between Profibrotic Fibroblasts and Inflammatory Cells in Early Keloid Wound Healing

Project No.: NHRI-EX115-11435SI
P.I.: Chao-Kai Hsu/許釗凱
NHRI Researcher: Daw-Yang Hwang/黃道揚
Key Professional Personnel: Shih-Wei Jao/饒師維, Yi-Han Chang/張藝瀚
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Background and Objective

Keloids are fibroproliferative scars caused by dysregulated wound healing and are associated with pain, pruritus, cosmetic concerns, and functional impairment. Although chronic inflammation, fibroblast activation, and vascular remodeling have been implicated in keloid pathogenesis, the dynamic cell–cell communication programs during wound healing remain unclear. This project aims to identify keloid-prone signaling pathways by comparing wound-healing responses between healthy controls and keloid-prone patients.

Methods

Serial skin samples were collected using a biopsy–rebiopsy approach at Day 0, Day 2, and Day 42, representing pre-wounding, early wound-healing, and late wound-healing stages. Single-cell sequencing was performed to analyze changes in cellular composition and intercellular communication. CellChat was used to compare signaling activities and pathway enrichment between healthy and keloid-prone groups.

Preliminary Results

Single-cell analysis revealed dynamic changes in fibroblasts, keratinocytes, vascular endothelial cells, and macrophages during wound healing. At Day 42, the keloid-prone group showed increased proportions of vascular endothelial cells and keratinocytes. CellChat analysis showed higher incoming signaling activity in keratinocytes and increased outgoing signaling activity from fibroblasts and vascular endothelial cells in keloid-prone late-stage wounds. Comparative pathway analysis identified ACTIVIN and GALECTIN signaling as candidate pathways potentially associated with profibrotic matrix remodeling and fibrosis-related immune regulation.

Conclusion

These preliminary findings suggest that altered intercellular communication during late wound healing may contribute to keloid-prone scar formation. ACTIVIN and GALECTIN signaling may represent potential molecular programs involved in fibroblast activation, matrix remodeling, and fibrosis-associated immune regulation. Further analyses will focus on ligand–receptor interactions, profibrotic fibroblast populations, inflammatory cell subsets, chromatin accessibility by single-cell Multiome ATAC-seq, spatial transcriptomics, and immunostaining validation to further define keloid-associated signaling mechanisms and potential targets for early intervention.

Title of Project: Unraveling the Molecular Mechanisms of Non-Alcoholic Fatty Liver Disease (NAFLD) in Children Through a Diet-Induced NAFLD Animal Model

Project No.: NHRI-EX115-11436SI
P.I.: Chun-Mei Hu/胡春美
Key Professional Personnel: Dan-Ni Wu/吳丹霓, Chin-Chun Chang/張謹淳, Li-Wen Lee/李莉文
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Background & Aims: Pediatric steatotic liver disease (SLD) is a prevalent yet reversible condition, but early detection and clinical management are hindered by invasive diagnostics. We aimed to identify a non-invasive urinary biomarker signature for early-stage pediatric SLD and elucidate its underlying pathophysiological roles.

Methods: We integrated clinically relevant murine models with pH-dependent urine metabolomics to discover an SLD-associated metabolic signature. Diagnostic performance was evaluated in a clinical validation cohort of 218 children. Furthermore, we analyzed the correlation between these metabolites and gut microbiota, and conducted mechanistic evaluations to determine the direct impact of these metabolites on hepatic lipid dysregulation.

Results: A two-metabolite panel comprising urinary isobutyric acid and valine exhibited outstanding diagnostic accuracy for pediatric SLD (AUC = 0.955), retaining exceptionally high sensitivity even for mild, early-stage disease (AUC = 0.967). Crucially, this distinct metabolic signature was closely associated with gut microbiota dysbiosis, specifically correlating with the enrichment of *Lactobacillus* and *Clostridium*. Beyond their diagnostic utility, mechanistic evaluation revealed that these metabolites act as pathogenic drivers that actively promote hepatocellular lipid accumulation by stimulating de novo lipogenesis.

Conclusions: Urinary isobutyric acid and valine establish a highly accurate, non-invasive screening strategy for pediatric SLD. By linking these gut microbiota-associated metabolic alterations directly to hepatic lipid dysregulation, this study provides novel insights into SLD pathogenesis and identifies promising targets for clinical intervention.

Keywords: Pediatrics; Steatotic liver disease (SLD); Gut-liver axis; De novo lipogenesis; Early detection; Metabolomics; Urine biomarkers; Isobutyric acid; Valine; Dysbiosis.

Title of Project: Methyl Epigenome Repression of Osteoarthritis: Macrophage Extracellular Vesicle Action to Cartilage

Project No.: NHRI-EX115-11437SI
P.I.: Wei Shiung Lian/連韋雄
Key Professional Personnel: Wei-Shiung Lian/連韋雄, Re-Wen Wu/巫瑞文, Ching-Feng Cheng 鄭敬楓, Mei-Yao Lin 林美瑤
Affiliation/Institution: Chang Gung Medical Foundation
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Background: Osteoarthritis (OA) is considered as degenerative joint disease with low-grade chronic inflammation, demonstrating notable features, including synovial hyperplasia, cartilage erosion and pain. Macrophage-induced inflammation accelerates extracellular matrix degradation in chondrocytes, thereby inducing cartilage breakdown. Epigenetic histone methylation is correlated with OA development; however, the role of macrophage UTX-histone H3K27me3 demethylase in the joint microenvironment during OA remains uncertain.

Objectives: We investigate the association between macrophage UTX levels and human knee OA. To best understand the function of macrophage *Utx* in age- and trauma-induced joint integrity loss, we generate macrophage-specific *Utx* knockout mice (*Lyz2*^{Cre}-*Utx*^{loxP}). We also investigate the effect of *Utx*KO macrophages on extracellular matrix anabolism in inflamed chondrocytes.

Materials and Methods: Destabilized medial meniscus (DMM) was performed to induce OA features. Osteophyte formation, subchondral plate sclerosis, and trabecular network were instigated using a micro-CT platform. Mechanical allodynia and walking patterns were measured using electronic von-Frey analysis and CatWalk analysis, respectively. The severity of joint damage was evaluated using Safranin-O stain. Glycosaminoglycan synthesis of chondrocytes was investigated using Alizarin blue stain. Spatial transcriptome of bone-marrow was characterized using single-cell sequencing, and transcriptomic landscapes of macrophages were investigated using RNA sequencing.

Results: Increased UTX levels in CD86^{+} macrophages from peripheral blood and synovial tissue are correlated with human knee OA who undergo total knee arthroplasty. Myeloid-specific *Utx*KO mice demonstrate a relatively small stature and exhibit attenuated age-induced body adiposity and bone loss alongside OA-like signs, including articular cartilage loss, osteophyte formation, and subchondral plate sclerosis. Myeloid *Utx* loss delays the development of key OA in DMM-injured joints together with decreased serum cartilage breakdown products, thereby mitigating mechanical allodynia and irregular gait profiles. Spatial transcriptomic landscapes reveal that *Utx* deletion represses monocyte/macrophage abundance, particularly Nkfbiz-dependent immune response and extracellular matrix metabolism. In a co-culture model, *Utx*KO macrophages reverse glycosaminoglycan production of inflamed chondrocytes. *Utx* loss alters transcriptomic profiles that contribute to macrophage chemotaxis, extracellular exosome release, and the negative regulation of TNF production. Notably, inhibition of extracellular vesicle synthesis by GW4689 offsets the chondroprotective effect of *Utx*KO macrophages on inflamed chondrocytes.

Conclusions: Collective analyses demonstrate macrophage UTX loss in human knee OA. *Utx* loss shift monocyte/macrophage profile in bone-marrow microenvironment that protects extracellular matrix biosynthesis of inflamed chondrocytes, thereby delaying cartilage breakdown and OA development. Our findings highlight the cartilage-regulatory function of the epigenetic regulator *Utx* in macrophages within degenerative joints.

Title of Project: Engineered Molecular Warheads Target Virus-Infected Mosquitoes
Project No.: NHRI-EX115-11438SI
P.I.: Ming-Jiun Yu/余明俊
Key Professional Personnel: Ming-Jiun Yu/余明俊
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Aedes aegypti remains a formidable vector for Flaviviridae pathogens like dengue and Zika viruses. Traditional control methods often rely on indiscriminate population suppression, which can disrupt ecosystems and drive insecticide resistance. We developed VOUDOU (Virus-Operated Up- or Down-expression of yOUr gene), a modular genetic platform that converts viral infection into a programmable transcriptional command. By coupling a virus-specific NS3 protease-responsive switch with the yeast Gal4-UAS system, VOUDOU acts as a "dormant sentinel" triggered only by the pathogen. We optimized the circuit's precision using a *Drosophila* Synthetic Core Promoter (DSCP), which reduced basal leakiness by 80% compared to the Hsp70 promoter. Validation in *Aedes aegypti* cells confirmed the system's versatility: up-regulating the neuropeptide leucokinin significantly increased fluid secretion in Malpighian tubules, while VOUDOU-mediated expression of a microRNA targeting ATP synthase subunit b (ATPB) successfully starved the virus of metabolic resources. This targeted interference resulted in a marked reduction of viral RNA synthesis. Importantly, our data demonstrate that even fractional cleavage of the VOUDOU sensor is sufficient to drive robust Gal4-mediated expression. By selectively reducing cellular hospitality only within infected individuals, VOUDOU offers a surgical strategy to curtail transmission without the need to kill the vector. This framework provides an ecologically sustainable approach for both strategic vector control and fundamental research into insect biology and host-pathogen dynamics.

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: Alice Lin/林倩如, Neng-Yu Lin/林能裕, Cheng-Chang Chen/陳政彰

Affiliation/Institution: National Taiwan University

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

Endolysosomal ion channels regulate vesicular trafficking, host defense, organelle remodeling, and disease-associated cellular responses. However, direct functional analysis of intracellular organelle channels has long been limited by technical barriers. The major goal of this NHRI-supported project was to establish and apply novel intracellular organelle patch-clamp and calcium imaging approaches to study endolysosomal cation channels, particularly TPC2 and TRPML2, in immune and disease-related cellular contexts.

During the project period, we successfully established a whole-endolysosome patch-clamp platform in Taiwan and integrated it with genetically encoded calcium nanodomain imaging, live-cell organelle tracking, molecular modeling, and pharmacological modulation. These approaches enabled direct measurement of ion channel activity from individual intracellular vesicles and provided a functional framework to connect channel gating, organelle dynamics, and disease-relevant cellular behavior.

As a representative outcome of this platform, our recent study accepted by *Nature Communications*, entitled “O-linked glycan-dependent gating of TPC2 controls lysosomal excitability and organelle remodeling,” identified mucin-type O-linked glycosylation as a previously unrecognized regulatory mechanism of the lysosomal cation channel TPC2. We found that TPC2 carries O-linked glycans at two conserved luminal pore-loop residues, Ser612 and Ser613. Genetic disruption of O-glycan elongation by C1GALT1 knockdown or knockout, pharmacological inhibition of O-glycosylation, or direct mutation of Ser612/Ser613 markedly enhanced basal and agonist-evoked TPC2 activity. Whole-lysosome electrophysiology further demonstrated increased Ca^{2+} and Na^{+} conductance in glycan-deficient TPC2, indicating that luminal O-glycans function as a structural gating brake that restrains lysosomal excitability.

Mechanistically, molecular dynamics simulations suggested that glycosylation at Ser613 stabilizes the domain II luminal loop and restricts ion access to the pore entrance. Removal of this glycan increased loop flexibility and facilitated ion permeation. Functionally, TPC2 hyperactivation induced lysosomal tubulation, altered vesicle mobility, promoted TPC2 clustering, and enhanced migration and adhesion in cancer-related cellular models. These phenotypes were reversed by TPC2 inhibitors, including tetrandrine and the synthesized analog SC-3, supporting a causal link between glycan-dependent TPC2 gating and cellular behavior.

Together, this NHRI-supported work demonstrates the power of intracellular organelle electrophysiology for discovering disease-relevant regulatory mechanisms of endolysosomal ion channels. The study extends the concept of glycan-dependent ion channel regulation from the plasma membrane to the lysosomal system and provides a mechanistic foundation for future investigation of lysosomal excitability in infection, inflammation, cancer, and hematological malignancies.

Title of Project: Decode the Anti-inflammatory Effects of the Hypoxia-inducible Factor Prolyl-hydroxylase Inhibitor

Project No.: NHRI-EX115-11517SC
P.I.: Szu-Yu Pan/潘思宇
Key Professional Personnel: Szu-Yu Pan/潘思宇
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2026 to 2029 (Total: 4 years)

Hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs) are novel drugs approved to treat anemia in patients with chronic kidney disease (CKD). In addition to promoting erythropoiesis, HIF-PHIs may exert biological effects relevant to the clinical care of patients with CKD.

We used *Tg(UBC-CreERT2);Egln1*$^{F/F}$ mice and the adenine nephropathy model to mimic HIF-PHI treatment in patients with CKD. After tamoxifen induction, *Tg(UBC-CreERT2);Egln1*$^{F/F}$ mice had global deletion of *Egln1*, which encodes the major HIF prolyl-hydroxylase in the kidney. This model successfully recapitulated the clinical effects of HIF-PHIs, including increased plasma erythropoietin, splenomegaly, and increased hematocrit. Importantly, we observed significant attenuation of kidney injury (*Havcr1* mRNA), reduced inflammatory cytokine expression (*Ccl2* and *Cx3cl1* mRNA) in the kidney, reduced expression of adhesion molecules (*Vcam1* and *Icam1* mRNA) in the kidney, and reduced kidney-infiltrating leukocytes. Single-cell RNA sequencing analysis of isolated kidney-infiltrating leukocytes also suggested alterations in the composition of these infiltrating immune cells.

Prior studies have also reported that global HIF overexpression attenuates kidney inflammation in genetic mouse models (*Tg(UBC-CreERT2);Vhl*$^{F/F}$) or after treatment with the HIF-PHI roxadustat. Because both *Egln1* and *Vhl* deletion result in stabilization of both HIF-1 and HIF-2, we generated *Tg(UBC-CreERT2);Vhl*$^{F/F}$*;Hif1a*$^{F/F}$ mice (selective HIF-2 overexpression) and *Tg(UBC-CreERT2);Vhl*$^{F/F}$*;Hif2a*$^{F/F}$ mice (selective HIF-1 overexpression) to examine the specific roles of HIF-2 and HIF-1 in the anti-inflammatory effects. In the adenine nephropathy model, only *Tg(UBC-CreERT2);Vhl*$^{F/F}$*;Hif1a*$^{F/F}$ mice, but not *Tg(UBC-CreERT2);Vhl*$^{F/F}$*;Hif2a*$^{F/F}$ mice, had reduced kidney-infiltrating leukocytes.

The mechanism by which global HIF-2 overexpression attenuates kidney inflammation may involve either cell-intrinsic HIF-2 overexpression or indirect effects through modulation of the inflammatory microenvironment. Because HIF-2 expression is largely limited to endothelial cells and fibroblasts in the kidney, we will use mice with HIF-2 expression restricted to endothelial cells or fibroblasts to examine their contributions to HIF-2-mediated suppression of kidney inflammation and leukocyte recruitment.

Title of Project: Investigate the Role of Nfic in Immune-cardiac Interaction During Heart Regeneration

Project No.: NHRI-EX115-11534SI
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, Kah-Wei Tee/鄭家威
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2026 to 2028 (Total: 3 years)

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

Myocardial infarction (MI) causes irreversible cardiomyocyte (CM) loss and adverse cardiac remodeling, frequently leading to heart failure and death. By contrast, adult zebrafish regenerate their hearts efficiently through a coordinated sequence of immune activation, cardiomyocyte dedifferentiation and proliferation, neovascularization, and scar resolution. Although immune activation is known to precede cardiomyocyte replenishment, the upstream transcriptional mechanisms that translate inflammatory cues into regenerative responses remain largely unknown.

To identify these regulatory mechanisms, this study employed regenerative zebrafish and non-regenerative medaka as complementary models and integrated comparative time-series transcriptomic datasets to construct a regeneration-specific Time-Ordered Gene Coexpression Network (TO-GCN). Comparative network and pathway analyses revealed that successful heart regeneration is orchestrated through sequential regulation of cellular metabolism, cell-cycle activation, and a coordinated transition from innate to adaptive immune responses. Using network topology, promoter binding predictions, and evolutionary conservation, we identified candidate upstream TFs, including *sox3*, *nfic*, *tfap2c*, *srebf1*, *tal1*, and *rfx5,* as key regulators of regeneration-associated cardiomyocyte gene programs.

We subsequently validated these candidates through a three-tiered experimental strategy. First, in situ hybridization and cardiomyocyte isolation confirmed reactivation of candidate TFs in dedifferentiated cardiomyocytes following injury. Second, CRISPR/Cas9-mediated knockout demonstrated that loss of *sox3* or *nfic* impairs cardiomyocyte dedifferentiation and proliferation, resulting in delayed regeneration and increased fibrotic scarring. Third, cardiomyocyte-specific overexpression of Sox3 or Nfic enhanced proliferation, with Sox3 primarily promoting dedifferentiation and proliferation while Nfic predominantly drove proliferation, indicating distinct but complementary regulatory mechanisms. Notably, ectopic expression of these factors was sufficient to induce regeneration-related processes even under injury-free conditions, highlighting their potent pro-regenerative capacity.

To assess evolutionary conservation, knockdown experiments in neonatal mouse cardiomyocytes reduced proliferation, suggesting that these transcriptional programs are conserved across vertebrates.

Collectively, this study presents a comprehensive framework spanning network construction, key factor identification, and functional validation, revealing the transcriptional regulatory cascade downstream of immune initiation that governs cardiomyocyte regeneration. These findings establish the regeneration-associated TF TO-GCN as a powerful platform for interrogating heart regeneration mechanisms and provide a new molecular basis for therapeutic strategies aimed at promoting cardiomyocyte replenishment and treating myocardial infarction.

Title of Project: Investigate the Role of Nfic in Immune-cardiac Interaction During Heart Regeneration

Project No.: NHRI-EX115-11534SI
P.I.: Shih-Lei (Ben) Lai/賴時磊
Key Professional Personnel: Kah-Wei Tee/鄭家威
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2026 to 2028 (Total: 3 years)

Identification of NFIC as a Key Transcriptional Regulator in Vertebrates' Cardiac Regeneration

Myocardial infarction serves as the leading cause of death worldwide due to a lack of effective therapeutic strategies to restore the loss of cardiac tissue and function. Unlike mammals, adult zebrafish possess the ability to fully regenerate the heart after injury by the expansion of the pre-existing cardiomyocytes near the wound border zone through cardiomyocyte dedifferentiation and proliferation. Recent studies have shown that macrophages play an essential role in this regenerative process. Hence, to decipher the underlying mechanisms, we performed single-nucleus ATAC-sequencing in macrophage-depleted hearts versus regenerative controls and identified a potential regulator, Nuclear Factor I C (NFIC), as a macrophage-dependent transcription factor with motif selectively accessible in regenerative cardiomyocytes.

Consistently, *nfic* was transcriptionally reactivated upon injury, and co-localizing with dedifferentiated cardiomyocytes. While the *nfic* deficiency in zebrafish impairs the cardiomyocyte dedifferentiation and proliferation, whereas the myocardium-specific *nfic* expression drives cardiomyocyte proliferation even without injury. Notably, the conserved function of NFIC in cardiac regeneration was further supported in neonatal mice, where Nfic knockdown inhibited cardiomyocyte proliferation, suggesting an evolutionarily conserved role across vertebrates.

Together, these findings identified Nfic as a novel regulator linking immune activation to cardiomyocyte plasticity during heart regeneration. Future studies will focus on elucidating the cell-autonomous function and molecular mechanisms by which NFIC regulates cardiomyocyte regeneration through identification of downstream target genes and regulatory networks using cardiomyocyte-specific bulk RNA sequencing and epigenetic profiling . In addition, the relationship between immune activation and Nfic function during cardiac injury will be investigated, with emphasis on macrophage–cardiomyocyte crosstalk and computational inference of upstream signaling pathways driving Nfic activation. Lastly, the functional role of NFIC in mammalian systems will be investigated using human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and adult mouse models of myocardial infarction, to determine whether NFIC also promotes cardiomyocyte cell-cycle re-entry, dedifferentiation, and cardiac regeneration in non-regenerative vertebrates.

Title of Project: Roles of TRIM28 in Immune Aging and Its Therapeutic Modulation
Project No.: NHRI-EX115-11537SI
P.I.: Shunsuke Chikuma/竹馬俊介
Key Professional Personnel: Shunsuke Chikuma/竹馬俊介
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2026 to 2028 (Total: 3 years)

Aging causes functional decline of the immune system, referred to as Immune Aging. Immune aging leads to immune deficiency and inflammation, and accelerates mortality. The molecular mechanisms causing immune cell senescence, leading to Immune Aging have not been established. TRIM28 is a nuclear protein, essential for regulation of both gene expression and repression through chromatin regulation. We found that TRIM28 expression in T lymphocyte (T cells) and dendritic cell (DCs), decline upon aging (PMID: 33619215) In addition, genetic ablation of TRIM28 on immune cells cause immune aging phenotypes (PMID: 22544392). We present that TRIM28 is a critical factors for regulating immune tolerance in autoimmune and cancer setting. In this study, we try to elucidate a functional link between TRIM28 decline and immune aging phenotypes. Some preliminary data will be presented.

Title of Project: Innovative Dengue Subunit Vaccine Candidates Using Unconventional Circular RNAs (II)

Project No.: NHRI-EX115-11540SI
P.I.: Shu-Wen Wan/萬書玟
NHRI Researcher: Chia-Yi Yu/余佳益
Key Professional Personnel: Ting-En Liang/梁庭恩, Chan-I Su/蘇沛晴, Zih-Shiuan Chuang/莊子萱, Hsin-I Wang/汪欣儀
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2026 to 2028 (Total: 3 years)

Despite extensive vaccine development efforts, dengue virus (DENV) infection remains a major global threat due to concerns regarding vaccine safety and efficacy. The success of SARS-CoV-2 mRNA vaccines has strengthened confidence in RNA-based vaccine platforms, which offer greater flexibility than traditional protein vaccines in addressing antigen design challenges. We previously developed a multivalent dengue fusion protein, ΔcNS1-cEDIII-ΔnNS3, consisting of risk-reduced nonstructural protein 1 (NS1), the consensus envelope protein domain III (EDIII), and partial NS3 domains, to induce protective humoral and cellular immune responses. To overcome the limitations of recombinant protein production, we adapted our patented 3-in-1 DENV vaccine concept to a circular RNA (circRNA) vaccine platform. Our recent findings indicate that, following a single injection of circRNA, reporter proteins or the 3-in-1 antigen were consistently detectable at the injection site for at least 3 days, as evidenced by *in vivo* imaging system analysis and immunohistochemical staining. Moreover, immunization with circRNA encoding ΔcNS1-cEDIII-ΔnNS3 induced only a slight humoral immune response, accompanied by a robust cellular immune response. To improve its immunogenicity, we redesigned our circRNA-encoding immunogen by incorporating a transmembrane domain. Notably, the transmembrane-anchored circRNA vaccine encoding ΔcNS1-cEDIII-ΔnNS3 improved the immune response profile by inducing both humoral and cellular immunity. Future studies will further assess its protective efficacy against DENV infection and elucidate the immune mechanisms underlying circRNA vaccine-mediated protection.

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: Hsuan-Ti Wang/王媗棣
Affiliation/Institution: National Taiwan University

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

Direct Patch-Clamp Recording of *Salmonella*-Containing Vacuoles Reveals Functional TRPML2 Activity

Intracellular pathogens remodel host endomembranes to generate specialized pathogen-containing vacuoles, yet the ionic conductance of these compartments has remained largely inaccessible to direct electrophysiological analysis. *Salmonella enterica serovar Typhi* replicates within *Salmonella*-containing vacuoles (SCVs), where magnesium availability influences bacterial survival and host antimicrobial defense. TRPML2/MCOLN2 has been implicated in restricting Salmonella replication by limiting Mg^{2+} availability within SCVs, but direct functional evidence for TRPML2 activity on the SCV membrane has been lacking.

Here, we establish a direct patch-clamp approach for recording ionic currents from SCVs in infected THP-1 cells. Using this platform, we show that SCVs exhibit inwardly rectifying currents that are markedly reduced in TRPML2-deficient cells and potentiated by TRPML agonists, demonstrating functional TRPML2 activity on pathogen-containing vacuolar membranes. Under Mg^{2+}-permeant recording conditions, agonist-evoked Mg^{2+} currents were detected in wild-type vacuoles but were largely absent in TRPML2-deficient vacuoles, supporting TRPML2 as a Mg^{2+}-permeable channel during infection. In addition, basal current-rundown analysis suggests that the SCV membrane environment stabilizes TRPML2 activity, providing a possible mechanism by which pathogen-induced vacuole remodeling sustains ion-channel function.

Together, these findings provide direct electrophysiological evidence that TRPML2 mediates divalent cation conductance on SCV membranes and establish SCV patch-clamp as a platform for studying ion-channel physiology at the host–pathogen interface.

Title of Project: Defining the RNA-Binding Protein RBM24 Regulatory Network in Cardiomyopathy and Sarcomere Integrity

Project No.: NHRI-EX115-11538SI
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 2026 to 2028 (Total: 3 years)

RNA-binding proteins (RBPs) are increasingly recognized as critical modulators of cardiac development and pathology. Among them, RBM24 plays essential roles in cardiomyocyte development and sarcomere organization, yet the scope of its downstream effectors is not fully understood. Here, we identify HEY2, a transcription factor indispensable for ventricular morphogenesis, as a major downstream effector of RBM24.

Loss of RBM24 resulted in a marked reduction of *HEY2* expression and a pronounced alternation in its subcellular distribution. Ectopically expression of RBM24 in the knockout background restored both HEY2 level and localization, indicating that RBM24 is required to maintain proper HEY2 regulation. Mechanistically, RNA immunoprecipitation and enhanced crosslinked immunoprecipitation (eCLIP) analyses revealed direct binding of RBM24 to the HEY2 transcript. Consistently, mRNA decay assays demonstrated that RBM24 stabilizes HEY2 mRNA. In parallel, RBM24 deficiency disrupted the poly(A)-binding protein network, including PABPN1 and PABPC1, suggesting broader perturbation of mRNP organization.

Functionally, HEY2 knockout in hPSC-derived cardiomyocytes caused severe sarcomere disorganization, underscoring its essential role in maintaining cardiomyocyte structural integrity. Together, these findings uncover a previously unrecognized RBM24–HEY2 regulatory axis that integrates RNA stability and protein localization to control cardiogenesis, providing new mechanistic insight into congenital heart disease and may inform future therapeutic strategies.

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

Project No.: NHRI-EX115-11201NI
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

Cardiovascular disease represents the leading cause of excess mortality in schizophrenia, with atherosclerosis developing at accelerated rates through poorly characterized mechanisms. We hypothesized that schizophrenia-specific immune dysregulation, particularly monocyte/macrophage activation, contributes to atherosclerotic progression beyond metabolic and medication-related factors. This study aimed to examine which monocyte/macrophage phenotypes with specific surface markers and clinical features are associated with accelerated atherosclerosis.

Methods

This case-control study recruited 175 medically healthy schizophrenia outpatients (DSM-5 criteria, aged 20-50) and 110 healthy controls aged 20-50. Carotid intima-media thickness (CIMT) was assessed via high-resolution B-mode ultrasonography. Flow cytometry characterized circulating monocyte/macrophage lineage cells using M1 markers (CD80, CD86, CD284) and M2 markers (CD163, CD204, CD206). Comprehensive inflammatory and oxidative stress biomarkers were measured. Antipsychotic exposure was retrospectively quantified from illness onset.

Results

Schizophrenia patients exhibited significantly increased CIMT, high-sensitivity C-reactive protein, and monocyte-lymphocyte ratio compared to controls. Flow cytometry revealed increased frequencies of multiple activated monocyte/macrophage subsets. Multiple regression analysis, adjusting for age, smoking, and obesity, identified two specific phenotypes as primary CIMT predictors: CD14++CD16+CD80+ intermediate monocytes (expressing co-stimulatory molecule CD80) and CD14+CD16−CD11b+CD86+ macrophages (characterized by adhesion molecule CD11b and co-stimulatory CD86). Traditional cardiovascular risk factors and antipsychotic exposure duration showed no significant associations with CIMT.

Conclusions

These findings establish immune activation, particularly specific monocyte/macrophage phenotypes with enhanced inflammatory and adhesion properties, as central mechanisms underlying accelerated atherosclerosis in schizophrenia. The independence from medication effects suggests intrinsic disease-related immunopathology, highlighting potential immunotherapeutic approaches for cardiovascular risk reduction.

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

Project No.: NHRI-EX115-11207NI
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)

The A/T/N framework defines Alzheimer's disease (AD) by its core pathological features and describes a temporal progression from amyloid-β (Aβ) deposition to tau pathology, neurodegeneration, and cognitive decline. The transition from Aβ+/tau- to Aβ+/tau+ stages is a pivotal event that closely precedes symptom onset, yet the mechanisms underlying this transition remain unclear. Through glia-specific transcriptomic network analyses of the ROSMAP and MAYO cohorts, we identified EAAT2 as a key regulator of AD-associated gene expression. Astrocytic glutamate transporters EAAT1 and EAAT2 (GLAST and GLT-1 in rodents) are essential for maintaining glutamate homeostasis and preventing excitotoxicity. We hypothesized that impairment of these transporters promotes excitotoxicity and accelerates tau pathology. To test this hypothesis, we used 3xTg-AD and 5xFAD mouse models and performed astrocyte-specific gain- and loss-of-function manipulations of GLAST and GLT-1. Behavioral, molecular, and histopathological analyses were conducted, and excitotoxicity was induced with kainic acid to determine its causal role in tau pathology. We also evaluated the therapeutic potential of two AI-predicted glutamate transporter-enhancing compounds. In parallel, the impact of insulin signaling on transporter expression was examined using insulin-resistant astrocytes and astrocyte-specific insulin receptor deletion models. Aged 3xTg-AD mice exhibited reduced hippocampal GLAST expression, cognitive impairment, and progressive tau pathology. Astrocyte-specific knockdown of GLAST or GLT-1 worsened memory deficits, increased calpain activation and p25/Cdk5 signaling, and aggravated tau pathology without affecting amyloid burden. Conversely, overexpression of either transporter reduced excitotoxicity, improved cognition, and attenuated tau pathology. Kainic acid-induced excitotoxicity increased Cdk5 activation and tau hyperphosphorylation without altering amyloid deposition, demonstrating a direct role of excitotoxicity in driving tau pathology. In 5xFAD mice, amyloid accumulation was associated with reduced GLAST and GLT-1 expression, particularly in females. Systemic treatment with the two AI-predicted compounds increased transporter expression, reduced excitotoxicity, improved cognition, and ameliorated both amyloid and tau pathology, partly through enhanced microglial Aβ phagocytosis. Additionally, impaired insulin signaling reduced GLAST and GLT-1 expression *in vitro* and *in vivo*. Together, these findings identify glutamate transporter dysfunction as a critical link between amyloid pathology and tauopathy and highlight EAAT1/2-mediated glutamate clearance as a promising therapeutic target for delaying AD progression.

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

Project No.: NHRI-EX115-11303NI
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 2.5 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 and T-type calcium 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. Therefore, the model predicts that *Grid2*^{dupE3} mice do not respond to propranolol or T-type calcium channel blockers. We have performed preclinical drug trials and validated model predictions. Furthermore, we have developed a new biomarker: Frequency dynamic index (FDI), which allows us to separate harmaline and *Grid2*^{dupE3} mice based on electrophysiological signatures.

In the final year, we will complete the biomarker validations in ET patients and submit this paper.

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

Project No.: NHRI-EX115-11309NI
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)

Vagal afferents transmit internal sensory signals from the body to the brain, thereby regulating vital bodily functions. However, the central dissemination of function-specific vagal afferent information remains largely unexplored. Here, we monitor *in vivo* calcium dynamics to provide direct evidence for distinct vagal sensory pathways that detect sucrose and the inflammatory mediator interleukin-1β (IL-1β). Using activity-dependent genetic capture of vagal neurons activated by sucrose or IL-1β, we demonstrate the existence of separate vagal-brainstem interoceptive circuits that sense these stimuli and, in turn, control sucrose consumption and elicit anxiety-like behavior. Genetic silencing of these vagal-brainstem interoceptive circuits effectively suppresses the corresponding behavioral responses. Short-term high-fat diet feeding alters the function of both sucrose- and IL-1β-sensing vagal-brainstem circuits. These findings offer deeper insight into how distinct vagal-brainstem interoceptive circuits convey appetitive and aversive sensory signals to the brain, underscoring the role of function-specific vagal afferent information in regulating bodily functions.

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-EX115-11310NI
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 examined the effects of a 12-week course of methylphenidate treatment on neural activity and behavioral problems in children with ADHD, aiming to identify biomarkers associated with treatment-related changes.

Method: 62 children with ADHD and 68 typically developing controls (TDCs) have been recruited. Behavioral symptoms and cognitive performance were evaluated using the ADHD Rating Scale-IV (ADHDRS-IV), Clinical Global Impression–Severity scale (CGI-S), Child Behavior Checklist (CBCL), and Swanson, Nolan, and Pelham Rating Scale – Fourth Edition (SNAP-IV). Children with ADHD received methylphenidate treatment for 12 weeks. Resting-state electroencephalography (EEG) was performed in both the ADHD and TDC groups before treatment and again after the 12-week follow-up to assess changes in brain activity.

Results: After 12 weeks of methylphenidate treatment, children with ADHD showed significant improvements in clinical symptoms and behavioral functioning. ADHDRS-IV scores, including inattentive and hyperactive/impulsive symptoms, were significantly reduced, and CGI ratings indicated overall symptom improvement. CBCL results demonstrated decreases in aggressive behavior, delinquent behavior, attention problems, social problems, and externalizing problems. Similarly, SNAP-IV scores showed significant reductions in inattention, hyperactivity/impulsivity, and oppositional symptoms, suggesting broad benefits of methylphenidate treatment on behavioral, emotional, and social regulation. EEG analyses revealed elevated low-frequency (δ, θ, α) power at baseline, which decreased following treatment, indicating modulation of cortical activity. Brain network analyses showed reduced clustering coefficients after treatment, suggesting improved global integration and normalization of excessive local connectivity. Regional network changes included increased frontal eigenvector centrality and reduced compensatory parietal involvement, reflecting enhanced frontal engagement and a more balanced pattern of functional brain organization.

Conclusions: These results underscore that ADHD is not merely a behavioral disorder, but also reflects underlying dysfunction in neural integration, cortical regulation, and large-scale brain network organization. The therapeutic effects of methylphenidate were evident not only in the improvement of core clinical symptoms, including inattention and hyperactivity/impulsivity, but also in measurable changes in brain function. Specifically, treatment appeared to rebalance abnormal cortical activity, reduce excessive local connectivity, enhance frontal network engagement, and improve the efficiency of neural information transmission. These neurophysiological changes suggest that methylphenidate may help restore more adaptive patterns of brain regulation in children with ADHD. Overall, our findings provide important evidence that pharmacological treatment acts through both behavioral and neural mechanisms. They also support the potential value of EEG-based brain network markers as objective indicators of treatment response, laying a foundation for future precision medicine approaches in ADHD.

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

Project No.: NHRI-EX115-11330NI
P.I.: Jun-An Chen/陳俊安
Key Professional Personnel: Fang-Yu Hsu/許芳瑜, Ya-Ping Yen/顏雅萍, Hung-Chi Fan/范宏綮, Mien Chang/張綿, Jun-An Chen/陳俊安
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Sertm2 is a conserved micropeptide that promotes GDNF-mediated motor neuron subtype specification

Small open-reading frame-encoded micropeptides within long noncoding RNAs (lncRNAs) are often overlooked due to their small size and low abundance. However, emerging evidence links these micropeptides to various biological pathways, though their roles in neural development and neurodegeneration remain unclear. Here, we investigate the function of murine micropeptide Sertm2, encoded by the lncRNA A730046J19Rik, during spinal motor neuron (MN) development. Sertm2 is predicted to be a conserved transmembrane protein found in both mouse and human, with subcellular analysis revealing that it is enriched in the cytoplasm and neurites. By generating C terminally Flag-tagged Sertm2 and expressing it from the A730046J19Rik locus, we demonstrate that the Sertm2 micropeptide localizes in spinal MNs in mice. The GDNF signaling-induced Etv4^{+}motor pool is impaired in Sertm2 knockout mice, which display motor nerve arborization defects that culminate in impaired motor coordination and muscle weakness. Similarly, human SERTM2 knockout iPSC-derived MNs also display reduced ETV4^{+} motor pools, highlighting that Sertm2 is a novel, evolutionarily conserved micropeptide essential for maintaining GDNF-induced MN subtype identity.

Title of Project: Investigating the Functional Roles of Novel Centrosomal Proteins Associated with Lissencephaly- and Microcephaly-Related Neurodevelopmental Disorders

Project No.: NHRI-EX115-11405NI

P.I.: Jin-Wu Tsai/蔡金吾

Key Professional Personnel: Meng-Han Tsai/蔡孟翰, Yu-Ching Liao/廖昱晴, Nian-Hsin Chao/趙年欣, Yu-Syuan Chang/張玉玄, Tzu-Wei Lin/林子崴, I-Hsuan Lin/林宜璇, Pei-Shan Hou/侯珮珊, Won-Jing Wang/王琬菁

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2025 to 2028 (Total: 4 years)

Background: The centrosome is a critical regulator of cortical development, orchestrating microtubule dynamics, cell cycle progression, and neuronal migration. Disruptions in centrosome-associated proteins have been associated with a range of neurodevelopmental disorders. CEP170, a microtubule-binding protein localized to the subdistal appendages (SDA) of centrioles, has been implicated in centrosome function, yet its role in corticogenesis remains poorly defined.

Methods: We analyzed CEP170 expression in mouse cortex using western blotting, qPCR, scRNA-seq, and spatial transcriptomics, and examined its transcript expression in the developing human cortex using scRNA-seq. Loss-of-function phenotypes were assessed via *in utero* electroporation of Cep170-targeting shRNAs in embryonic mouse cortex. Cell proliferation and microtubule dynamics were analyzed using CRISPR/Cas9-generated CEP170-knockout cells, flow cytometry, microtubule regrowth assays, and immunofluorescence microscopy. Protein interactions were examined via co-immunoprecipitation and subcellular localization studies.

Results: We show that CEP170 is expressed in both neural progenitors and postmitotic neurons during cortical development. Cep170 knockdown in embryonic mouse cortex resulted in profound neuronal migration deficits, altered laminar fate, and abnormal dendritic morphology. CEP170 depletion also impaired progenitor cell proliferation both *in vitro* and *in vivo*. Mechanistically, C-terminal truncations disrupted CEP170 centrosomal and microtubule localization, mediated via impaired interactions with CCDC120. These truncations impaired microtubule regrowth and organization. Strikingly, partial deletion of CEP170's centrosomal targeting and microtubule-binding domains led to severe migration deficits in the developing cortex.

Conclusion: Our findings identify CEP170 as a critical regulator of neural progenitor proliferation, neuronal migration, and cortical architecture via centrosome-microtubule interactions, providing new insights into centrosome-linked neurodevelopmental disorders.

Keywords: CCDC120; CEP170; Centrosome; Lissencephaly; Microcephaly; Microtubule organization; Neural progenitor; Neuronal migration.

Title of Project: Decoding Novel Mechanisms and Functions of Brain Imprintome: Applications to Mental and Neurological Disorders

Project No.: NHRI-EX115-11406NI
P.I.: Hsien-Sung Huang/黃憲松
Key Professional Personnel: De-Fong Huang/黃得峰
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Genomic imprinting is a special epigenetic mechanism contributing to parent-of-origin-specific genetic expression. Genomic imprinting predominantly occurs in brain and placenta; however, biological roles and underlying mechanisms of brain imprintome remain elusive. Moreover, deletions or mutations of imprinted genes cause several mental and neurological disorders. Therefore, there is an unmet need to investigate mechanisms and functions of the brain imprintome.

Through the support of the Career Development Grant from NHRI (NHRI-EX103-10316NC, 01/01/14-12/31/17), we established a solid foundation for investigating the brain imprintome as demonstrated by three publications. Moreover, through the support of the Innovative Research Grant from NHRI (NHRI-EX108-10802NI, 01/01/19-12/31/23), we provided a broad perspective and biological insights into the mechanisms and functions of the brain imprintome on a scale of whole genomes and single genes as demonstrated by five publications. To make best use of our accumulated research experience and resources in the brain imprintome over the past years, we propose to address a more difficult question in the field of the brain imprintome, which is: "**How does *Trappc9* demonstrate its isoform-specific imprinting status and what are the functional significances of such specificity?**".

To address this critical question, we are systematically generating multiple *Trappc9* mouse models, including conditional knockout (cKO) lines for isoforms 201 and 203, as well as distinct reporter lines (*Trappc9-203-GFP*, *Trappc9-203-tdTomato*, *Trappc9-201-smGFP*, and *Trappc9-201-mRuby2*). To achieve cell-type-specific deletion, Trappc9-201 and 203 cKO mice are being crossed with *Sox2-Cre* and *vGlut2-Cre* driver lines. Concurrently, we are establishing and optimizing a high-throughput platform for genome-wide screening in primary cortical neurons.

The significance of this grant proposal is that it would uncover novel mechanisms and functions of isoform-specific imprinting, which has yet to be identified. Moreover, our findings could provide new insights into how genomic imprinting operates in the brain and could apply to the understanding of the etiology in mental and neurological disorders, due to the association of these diseases with dysregulation of the brain imprintome.

Title of Project: Investigating the Pathogenic Mechanisms and Potential Therapeutic Targets of Free Fatty Acid Receptors in the Crosstalk Between the Gut and Nervous Systems in Parkinson's Disease

Project No.: NHRI-EX115-11407NI
P.I.: Chin-Hsien Lin/林靜嫻
Key Professional Personnel: Wei-Li Wu/吳偉立, Hung-Chih Kuo/郭紘志
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Short-chain fatty acids (SCFAs) are major gut microbiota–derived metabolites that link diet and metabolism to host physiology and are generally considered to exert beneficial health effects. However, their role in Parkinson's disease (PD)-related neurodegeneration remains incompletely defined. Here, we identify a mechanistic pathway by which SCFAs exacerbate PD pathology in a genetically susceptible background. We observe that the cerebrospinal fluid (CSF)-to-plasma SCFAs ratio, particularly propionate (C3), is elevated in patients with PD compared with unaffected controls. This ratio correlates with CSF α-synuclein seeding activity, supporting a clinically relevant association between peripheral metabolic signals and central protein aggregation. In neuronal models, SCFAs, but not long-chain fatty acids, enhance α-synuclein expression through activation of neuronal free fatty acid receptor 3 (FFAR3). Genetic knockdown and pharmacological inhibition of FFAR3 abolishes these effects *in vitro*. Mechanistically, SCFAs induce upregulation of the E3 ubiquitin ligase tetratricopeptide repeat domain 3 (TTC3), which promotes polyubiquitination and degradation of the transcriptional repressor CEBPδ. This process relieves repression of the *SNCA* promoter and drives progressive α-synuclein accumulation. *In vivo*, chronic high-dose, but not low-dose, intraperitoneal administration of SCFAs aggravates PD neuropathology and worsens locomotor function in transgenic *SNCA* p.A53T mice. Whole-brain transcriptomics analysis revealed that although SCFAs attenuate the expression of genes associated with neuroinflammation, they significantly suppress gene expression related to mitochondrial and lysosomal function, as well as proteasomal degradation pathways. Genetic ablation of FFAR3, but not FFAR2, abolishes these effects *in vivo*. Furthermore, chronic SCFA exposure induces region-specific neuronal activation in several brain regions, including nucleus tractus solitarius (NTS) and the paraventricular thalamus (PVT). Chemogenetic inhibition of the PVT, but not the NTS, mitigates chronic high-dose SCFAs-induced motor dysfunction and PD neuropathology in *SNCA* p.A53T mice. In conclusion, our findings define a metabolite-driven mechanism linking gut-derived SCFAs to α-synucleinopathy through FFAR3–TTC3–CEBPδ-dependent transcriptional regulation in a genetically susceptible *SNCA* mutant background. We further identify PVT as a responsible node mediating peripheral metabolite-induced PD pathology. Our results provide a framework for understanding gene–gut environment interactions in PD and highlight the FFAR3–TTC3–CEBPδ pathway as a potential therapeutic target.

Title of Project: Explore the Impacts of One Session and Multiple Session Theta Burst Stimulation over Cerebellum in Adults with Autism Spectrum Disorder

Project No.: NHRI-EX115-11419NC
P.I.: Hsing Chang Ni/倪信章
Key Professional Personnel: Hsing Chang Ni/倪信章
Affiliation/Institution: Chang Gung Medical Foundation
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Background: This four-year project investigates the effects of cerebellar theta burst stimulation (TBS) in autism spectrum disorder (ASD). Phase I evaluated the effects of single-session intermittent (iTBS) and continuous TBS (cTBS) on default mode network (DMN) connectivity and motor evoked potentials (MEPs) in autistic and healthy adults. Phase II is a randomized, placebo-controlled trial assessing the effects of 10-session cerebellar TBS on clinical symptoms, neuropsychological outcomes, and MRI measures in ASD. Phase I has been completed.

Method: In Phase I, we recruited 26 autistic adults and 27 healthy controls. Each participant received one session of intermittent theta burst stimulation (iTBS) and one session of continuous theta burst stimulation (cTBS) over the right cerebellum (Crus I/II) in a randomized crossover design, with a one-week washout interval between sessions. Resting-state MRI was performed before and after stimulation to assess changes in default mode network (DMN) connectivity. Motor evoked potentials (MEPs) elicited from the primary motor cortex (M1) were measured at baseline and at 5, 10, 15, and 20 minutes following cerebellar stimulation. 25 autistic adults and 25 healthy controls completed.

Results: Preliminary analyses (21 ASD and 24 TDC) of MEPs showed no significant changes following either iTBS or cTBS, whether autistic and healthy participants were analyzed together or separately. No significant interaction was observed between stimulation protocol (iTBS vs. cTBS) and time, and no three-way interaction among diagnosis (ASD vs. healthy control), stimulation protocol, and time was detected. Trajectory analysis identified a single response trajectory for all conditions. Analyses of inter-individual variability and default mode network connectivity are currently ongoing, with completion anticipated by September.

Conclusion: These preliminary trajectory findings suggest that cerebellar iTBS may induce heterogeneous neurophysiological responses in autistic adults, with a subset showing increased corticospinal excitability despite the absence of significant group-level effects. Ongoing analyses will compare DMN connectivity changes after iTBS and cTBS between autistic adults and typically developing controls, and relate these findings to MEP response patterns. Based on these results of stage I of this project, we will initiate the stage II double-blind sham-controlled randomized clinical trial for autistic adults using the personalized lateral cerebellar TBS protocol.

Title of Project: The Neurochemistry of Dopamine Systems in Amphetamines: Bridging Imaging Genetics with Genetic Neuropathology
Project No.: NHRI-EX115-11420NC
P.I.: Shyh-Yuh Wei/魏士郁
NHRI Researcher: Yen-Feng Lin/林彥鋒
Key Professional Personnel: Tzu-Yun Wang/王姿云, Chih-Hsin Pan/潘至信
Affiliation/Institution: National Cheng Kung University Hospital
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Blood Neurofilament Light Chain as a Biomarker of Functional Network Dysregulation and Risk of Relapse in Methamphetamine Use Disorder: A Multi-Modal Investigation with Clinical Implications

Aim: There is a critical need for objective biomarkers that can link peripheral assays to central neural network dysfunction. We investigated blood neurofilament light chain (NfL), a marker of axonal injury, and C-reactive protein (CRP), a marker of systemic inflammation, in relation to the brain network topology in methamphetamine use disorder (MUD), a paradigm of acquired neurotoxicity.

Methods: Forty-two male MUD patients and 44 male controls underwent analysis of blood NfL and CRP levels. We used graph theory to assess brain network topology and examined its correlation with NfL and CRP levels.

Results: Compared to controls, MUD patients exhibited significantly elevated blood NfL and CRP levels, as well as salience network dysfunction. Among MUD patients, higher NfL levels were associated with lower local efficiency in the right anterior insula, while higher CRP levels were associated with longer average path length in the bilateral supramarginal gyrus. Crucially, the correlation involving NfL levels remained significant after controlling for the duration of methamphetamine use, whereas the correlations involving CRP levels did not, indicating two distinct pathological processes. Furthermore, higher baseline NfL levels were significantly correlated with greater urine positivity rates during one-year follow-up.

Conclusions: Our findings support a two-pathway model in MUD, distinguishing a duration-independent neurotoxic process affecting local integration from a duration-dependent inflammatory process impairing diffuse integration. Collectively, this study suggests that blood NfL is not merely a marker of injury but a peripheral proxy for its functional consequences on a core addiction network, advancing the development of biomarkers for precision psychiatry.

Title of Project: Protective Effects of Human Platelet Lysates on CNS White Matter Damages
Project No.: NHRI-EX115-11431NI
P.I.: Thierry P. R. Burnouf/白台瑞
Key Professional Personnel: Le Thao Ngoc Nhi, Kirti Gupta, Abinaya Srinivasan, Mdlovu Ncobile Bagezile, Ming-li Chou/周明莉
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Central nervous system (CNS) white-matter damage is a major feature of demyelinating, neuroinflammatory, traumatic and age-related neurological disorders. Myelin loss, oligodendrocyte dysfunction, oxidative injury and persistent inflammation impair axonal conduction and limit neurological recovery. The NHRI-funded project "*Protective effects of human platelet lysates on CNS white matter damage*" investigates whether clinical-grade human platelet-derived preparations can provide a safe, scalable biotherapy to protect white matter and support CNS repair.

Human platelet pellet lysate preparations, including heat-treated platelet lysate (HPPL), and platelet-derived extracellular vesicles (pEVs) were produced from outdated platelet concentrates collected from healthy blood-donors and using standardized procedures compatible with clinical translation. These preparations contain platelet trophic factors, antioxidant and anti-inflammatory mediators, and EV-associated signals. Their activity was evaluated in cellular, *ex vivo* and *in vivo* models relevant to neuroprotection, neurogenesis, neuroinflammation and myelin integrity.

In a $ZnSO_4$-induced olfactory injury mouse model of transient anosmia, intranasal HPPL improved olfactory behavior, reduced microglial activation, and restored myelin binding protein (MBP)-associated myelin structures in the olfactory bulb. In a systemic inflammatory LPS/MOG mouse model of immune-mediated demyelination, intranasal HPPL attenuated cerebellar white-matter damage, reduced systemic and CNS-associated inflammatory neutrophil responses, limited splenic hypertrophy, and improved behavioral outcomes, including mobility and sucrose preference.

Mechanistic studies further support a role of platelet-derived trophic factors in white-matter repair. Proteomic analysis of dentate gyrus tissue of mice receiving intranasal pEV treatment 3 times per week over 28 days, identified 111 differentially expressed proteins and showed enrichment of pathways related to oxidative phosphorylation, respiratory electron transport, Notch4 signaling, myelination, ubiquitination and immune regulation. These findings suggest that platelet-derived preparations may support the metabolic, inflammatory and structural environment needed for myelin maintenance, neuronal maturation and circuit repair.

Together, these results indicate that intranasal acellular platelet-derived biotherapies can modulate key mechanisms involved in CNS white-matter injury, including neuroinflammation, oxidative stress, myelin disruption and endogenous repair. This NHRI-supported project provides a translational foundation for developing donor-derived platelet biologics for demyelinating and neuroinflammatory disorders such as multiple sclerosis, traumatic brain injury and age-related neurodegeneration.

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-EX115-11432NI

P.I.: Cheng-Chang Lien/連正章

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

GABAergic interneurons (INs) are a diverse population essential for shaping hippocampal circuit dynamics. Cholecystokinin-expressing (CCK) INs represent a major cannabinoid receptor type 1 (CB1R)-expressing subtype, traditionally characterized by their direct inhibition of principal neurons. However, their additional innervation of local INs suggests a circuit architecture capable of mediating disinhibition. Therefore, the functional impact of CCK IN recruitment and CB1R-dependent modulation on dentate gyrus (DG) output remains unclear.

Using *ex vivo* electrophysiology, pharmacology, and chemogenetic manipulations in the mouse DG, we show that CCK INs promote or suppress granule cell (GC) activity through distinct circuit mechanisms. CB1R activation suppresses GABA release from CCK INs and reduces GC responses to cortical input, whereas direct chemogenetic silencing of CCK INs enhances GC activity. These findings reveal a circuit-level interplay between direct inhibition and disinhibition mediated by CCK INs. We further demonstrate that, under baseline conditions, DG output is tuned by a balance between disinhibitory and inhibitory motifs involving CCK INs. CB1R activation selectively suppresses the disinhibitory component, thereby shifting the circuit toward a more inhibited state and reducing DG output. Together, these results identify CB1R signaling as a molecular switch that regulates disinhibitory circuit function, providing a mechanistic framework for cannabinoid control of hippocampal information gating.

Title of Project: Retrosplenial Cortex Microglia in Depression-like Behaviors
Project No.: NHRI-EX115-11504NI
P.I.: Margaret Ho/何淑君
Key Professional Personnel: Cheng-Chang Lien/連正章
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2026 to 2030 (Total: 5 years)

Major depressive disorder (MDD) is a prevalent neuropsychiatric disorder affecting millions of people worldwide. Current treatments are effective only for a subset of patients, reflecting our incomplete understanding of the underlying disease mechanisms. Although multiple neural circuits involved in memory, reward processing, and hypothalamic–pituitary–adrenal (HPA) axis regulation have been implicated in MDD, the cellular and circuit mechanisms driving disease onset and progression remain poorly understood. Increasing evidence identifies microglial activation and neuroinflammation as hallmarks of MDD; however, the contribution of microglia to depressive pathogenesis remains largely elusive.

Here, we identify the mouse retrosplenial cortex (RSC) as a key brain region involved in regulating depression-like behaviors. Wild-type and CX3CR1$^{+/GFP}$ mice subjected to chronic restraint stress (CRS) exhibited anhedonia, as demonstrated by reduced sucrose preference, accompanied by altered neuronal activity and microglial morphological changes in the RSC. Specifically, CRS reduced c-Fos expression predominantly in layer 5/6 RSC neurons, indicating decreased neuronal activity in these deep cortical layers. Furthermore, chemogenetic manipulation of RSC neuronal activity induced anhedonia, supporting a causal role for RSC neurons in regulating depression-like behaviors.

In parallel, RSC microglia displayed an activated morphology characterized by enlarged somata following CRS. Local administration of lipopolysaccharide into the RSC induced robust microglial activation and increased microglial density. Notably, chemogenetic activation of RSC microglia also elicited anhedonia, demonstrating that microglial activation within the RSC is sufficient to promote depression-like behaviors.

Together, these findings reveal that chronic stress induces coordinated layer-specific neuronal dysfunction and microglial activation in the RSC, highlighting neuron–microglia interactions as critical contributors to stress-induced depression. Our study identifies the RSC as a previously underappreciated brain region involved in the regulation of depressive-like behaviors and provides a foundation for elucidating the cellular and circuit mechanisms underlying MDD.

Title of Project: Investigate the Role of BF Glutamatergic Inputs to the Lateral Habenula in Rapid Behavioral Stopping

Project No.: NHRI-EX115-11514NI
P.I.: Shih-Chieh Lin/林士傑
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2026 to 2028 (Total: 3 years)

Rapid behavioral stopping, the ability to cancel an ongoing action, is essential for cognitive control and is impaired in ADHD, addiction, and compulsive disorders. We previously identified a population of basal forebrain (BF) GABAergic neurons, termed BF bursting neurons, whose inhibition immediately precedes stopping in a stop-signal task, making BF inhibition a reliable neural correlate of inhibitory control. However, the circuit mechanism responsible for this inhibition remains unknown. Here we show that BF Vglut2 neurons, particularly their LHb-projecting subset, suppress BF bursting neurons and provide a necessary and sufficient circuit mechanism for rapid behavioral stopping. Because BF Vglut2 neurons are implicated in negative-valence processing and project prominently to the lateral habenula (LHb), we first tested whether this pathway could inhibit BF bursting neurons. Optogenetic activation of BF Vglut2 neurons at either the soma or LHb axon terminals produced similar effects, rapidly inhibiting BF bursting neurons and transiently pausing behavior, thereby identifying LHb-projecting BF Vglut2 neurons as a candidate stopping circuit. We next established a freely moving stop-signal task in mice to determine whether this pathway is naturally recruited during stopping. Fiber photometry revealed distinct activity dynamics between BF Vglut2 somata and LHb-projecting axons: somatic activity was elevated during Go trials and increased after reward, whereas LHb terminal activity was selectively enhanced during Stop trials, particularly successful Stop trials. Bidirectional optogenetic manipulations further demonstrated that activation of BF Vglut2 neurons induced rapid stopping at short latencies, whereas inhibition selectively reduced stopping probability during Stop trials without comparable effects during Go trials, indicating that BF Vglut2 neurons are recruited for behavioral inhibition rather than motor execution. Terminal-specific manipulation of BF Vglut2 axons in the LHb produced similar behavioral effects, consistent with their preferential activation during successful stopping. Thus, despite functional heterogeneity among BF Vglut2 neurons, the LHb-projecting subset causally suppresses BF bursting neurons and promotes rapid behavioral stopping, establishing a previously unrecognized subcortical circuit for inhibitory control.

Title: Identification of Aging-Associated Alzheimer's Disease Risk Genes in the *Drosophila* Mushroom Body Through Integrative Single-Cell Transcriptomic Analysis

P.I. : Han-Hsuan Liu/劉翰璇
Presenter: Yi-Ting Hung/洪乙庭
Institute/Center : National Health Research Institutes

Aging is the strongest risk factor for Alzheimer's disease (AD), yet how aging reshapes AD-associated molecular programs remains poorly understood. Here, we integrated two publicly available whole-organism single-nucleus transcriptomic datasets- the Aging Fly Cell Atlas (AFCA) and the AD Fly Cell Atlas (AD-FCA)- to investigate whether AD accelerates normal aging-associated transcriptional programs in *Drosophila* brain. We focused our analysis on Kenyon cells and dopaminergic neurons, two key neuron types essential for learning and memory, with in male flies. Using the AD-FCA, we first identified 86 AD-associated genes that differentially expressed upon Aβ42 overexpression compared to control groups at both 10 and 20 days of age. We then compared these genes with aging-associated genes from the AFCA to identify overlapping molecular signatures between AD and normal aging. Finally, we compared age-dependent expression trajectories of 86 AD-associated genes between control and AD conditions to determine how AD pathology disrupts aging-associated transcriptional dynamics. Candidate genes will subsequently be manipulated in mushroom body output neurons (MBONs) to evaluate their effects on neuronal morphology and yeast-seeking behavior. Together, our findings demonstrate the utility of integrating public single-cell transcriptomic datasets to identify aging-associated AD candidate genes and prioritize targets for functional validation in the *Drosophila* brain.

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

Project No.: NHRI-EX115-11204BC

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)

Tight junctions are traditionally regarded as passive seals that maintain epithelial barrier integrity. Yet their scaffolding proteins also relay polarity cues to the mitotic apparatus, hinting at a broader role in tissue homeostasis. Building on our prior finding that the tight-junction protein ZO-1 (*TJP1*) makes junction-independent contributions to mitotic spindle orientation and mucosal repair, we hypothesized that ZO-1 functions as a molecular pivot, aligning the spindle with the basal surface matrix to safeguard against chromosomal instability (CIN), a recognized driver of colorectal cancer (CRC). Here we identify ZO-1 as a guardian of chromosomal integrity whose loss initiates genome-destabilizing events that precede and promote colorectal carcinogenesis.

Integrating human tissue analysis, a conditional knockout mouse model, and domain-resolved rescue in intestinal epithelial cells, we establish a causal link between ZO-1 dysfunction and CIN. In CRC specimens from National Taiwan University Hospital, immunofluorescence and qPCR revealed reduced ZO-1 protein and transcript relative to matched normal mucosa, accompanied by diminished E-cadherin and β-catenin and elevated PCNA and the DNA-damage marker p-H2A.X, coupling junctional disintegration to chromosomal instability. This signature was corroborated across global GEO datasets. Intestinal-specific ZO-1-null mice (ZO-1 KO^{IEC}) challenged with azoxymethane and dextran-sodium-sulfate developed high-grade dysplasia, downregulated E-cadherin and β-catenin, abundant p-H2A.X foci, and pronounced weight loss, providing direct *in vivo* evidence linking ZO-1 loss to genomic damage.

Mechanistically, CRISPR/Cas9-engineered ZO-1-null Caco-2 monolayers displayed spindle misalignment, sub-G1 apoptosis, and increased p-H2A.X. Domain-truncation analysis localized this protective activity to the ZO-1 N-terminus, whereas ablation of the ABR and U5-GuK domains restored correct spindle orientation. Notably, the phenotype coupled with DNA damage was refractory to inhibition of actin polymerization (latrunculin A, cytochalasin B, jasplakinolide), myosin II (blebbistatin), and ROCK (Y27632), dissociating it from ZO-1/actomyosin coupling. Instead, proximity-ligation assays revealed a spindle-associated interaction between ZO-1 and AKAP9, a regulator of microtubule dynamics, conserved across *in vitro* Caco-2 cells, *in vivo* murine tumors, and human patients. ZO-1 loss mislocalized and downregulated AKAP9, misaligned α-/γ-tubulin, and displaced the centrosome, mechanistically connecting tight-junction failure to spindle misorientation and DNA damage.

Collectively, these findings define ZO-1 as a protector of chromosomal stability whose N-terminal domain, acting through AKAP9, ensures faithful spindle alignment and limits DNA breakage. Its disruption destabilizes the genome, promotes colitis-associated tumorigenesis, and marks human CRC foci with a distinctive low-ZO-1/high-γ-H2A.X signature. By reclassifying tight-junction disassembly from a passive consequence of transformation to a proximal facilitator of malignancy, our work nominates the ZO-1/AKAP9 interface as a therapeutic target for intercepting genome-destabilizing early events in colorectal cancer.

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

Project No.: NHRI-EX115-11301BI

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 development for truly novel compounds remains limited by the cold-start problem, in which a new drug has few or no known links to targets, pathways, or diseases. Existing strategies usually attach a new node through chemical structure similarity or target sequence similarity. Although this strategy can provide an initial connection, it is still largely a static similarity-matching process and may miss the biological mechanism shared by structurally different drugs or overemphasize compounds that are chemically similar but mechanistically unrelated. Building on the Graph Transformer-Convolutional Network (GTCN), which models drugs, targets, pathways, and diseases as a heterogeneous graph, we propose a mechanism-aware dynamic cold-start framework for drug repurposing and new drug development. The framework first uses structure-based drug similarity as an initial pseudo-edge source and then introduces mechanism similarity derived from graph topology. Instead of relying on manually curated relation types, mechanism features are automatically extracted from typed shortest paths and meta-paths connecting drugs, targets, pathways, and diseases. These topology-derived features provide interpretable evidence of whether different drugs converge on related targets, pathways, or disease mechanisms. Furthermore, we design a dynamic expansion strategy in which high-confidence predicted drug-target relationships can be selectively fed back as reliable pseudo-edges for subsequent new-drug prediction. This allows the graph to be evaluated under both static and incremental settings while controlling potential error propagation by confidence thresholds. The proposed approach will be validated through leave-drug-out and sequential cold-start experiments, comparing conventional similarity-only baselines with mechanism-aware and dynamic-feedback models using target recovery, precision, recall, and interpretable path evidence. This study moves beyond simply adding a new node by similarity and aims to integrate chemical, topological, and mechanistic evidence for prioritizing candidate targets and therapeutic opportunities in cancer drug development.

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

Project No.: NHRI-EX115-11302BI

P.I.: Kuo-Chen Wei/魏國珍

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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 and molecular features of glioma while developing innovative therapeutic strategies to advance precision medicine for malignant brain tumors.

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 associated with poorer outcomes, underscoring the prognostic significance of TME composition.

To further investigate molecular determinants of glioma progression, we completed an extrachromosomal DNA (ecDNA) analysis comparing long- and short-survival glioma patients. The findings support a potential association between ecDNA alterations and glioma malignancy, providing new insights into disease progression and establishing a foundation for ongoing mechanistic studies and future publication.

In parallel, we developed a novel virus-like particle (VLP)-based nanobubble platform for sonodynamic therapy (SDT). Preclinical animal studies demonstrated promising therapeutic efficacy, supporting the feasibility of this targeted nanoplatform as a non-invasive therapeutic strategy for malignant glioma. These findings further highlight the potential of nanotechnology-enabled SDT for improving brain tumor treatment.

Together, our findings demonstrate that integrating tumor microenvironment profiling, ecDNA characterization, and innovative therapeutic platform development provides complementary insights into glioma biology and treatment. This multidisciplinary strategy advances precision medicine by identifying potential prognostic biomarkers and developing novel therapeutic approaches, offering new opportunities to improve the diagnosis and treatment of malignant brain tumors.

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

Project No.: NHRI-EX115-11306BI
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)

Self-association by small GTPases on membrane is critical for their signaling output and cellular function. However, a mechanistic understanding of how membrane components regulate this process remain incompletely understood. Here we show that phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) promotes Arl4D self-association to potentiate downstream Pak1 signaling. We first show that Arl4D self-association is GTP-dependent and occurs at the plasma membrane. Fibronectin stimulation increases this self-association through two cooperative mechanisms: i) direct binding of $PI(4,5)P_2$ by Arl4D via a conserved C-terminal polybasic motif, and ii) phosphorylation of Arl4D at Ser144 by its effector kinase Pak1. As a result, Arl4D membrane residency and protein stability are enhanced, with downstream signaling through Pak1 also amplified. Furthermore, pursuing structural prediction using AlphaFold, we generate an Arl4D mutant defective in self-association, but retains GTP binding and membrane targeting, and find that this mutant fails to activate Pak1 for cell migration, while forced self-association of this mutant restores these downstream effects. Collectively, our findings reveal how an extracellular matrix cue leads to directional cell migration through Arl4D assembling into signaling-competent multimers at the plasma membrane, with cooperation between lipid recognition and kinase-mediated feedback playing critical roles.

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

Project No.: NHRI-EX115-11307BC
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) represents a highly aggressive clinical phenotype defined by disease progression despite androgen deprivation therapy (ADT) and remains a primary cause of prostate cancer-related mortality. Building on our previous findings, we identified the transcription factor TEAD4 as a master regulator of therapeutic resistance. Our data indicate that TEAD4 drives this resistant state by modulating key epigenetic and metabolic landscapes. Specifically, ChIP-seq analysis of H3K27 acetylation (H3K27ac) revealed distinct, stage-specific epigenetic signatures in resistant models compared to parental lines. Notably, genetic ablation of TEAD4 abolished these H3K27ac alterations, underscoring its essential role in maintaining the epigenetic plasticity required for CRPC survival and progression. By further integrating the analysis of H3K27ac with TEAD4 ChIP-seq, we discovered that TEAD4 is associated with metabolic pathways involving steroid hormone metabolism and the ferroptosis pathway, indicating that its regulation of these metabolic pathways contributes to resistance.

To further elucidate the role of TEAD4 in acquisition of enzalutamide resistance, we performed longitudinal ATAC-seq analysis across sensitive, transition, and resistant stages. Our results demonstrate that while wild-type cells exhibit the phenotypic plasticity necessary to undergo "phenotypic switching" and survive drug pressure, TEAD4-deficient cells are incapable of developing resistance. Motif enrichment analysis further revealed that TEAD4 synergistically interacts with core lineage-specifying transcription factors, including FOXA1, HOXB13, and Fra1, to modulate stage-specific chromatin accessibility. This regulatory network is particularly enriched within transition-associated modules, suggesting that TEAD4 is a requisite driver of the epigenetic remodeling that facilitates the emergence of the resistant phenotype. Genetic ablation of TEAD4 disrupted these dynamic chromatin shifts, specifically causing a significant loss of distal intergenic accessibility during the transition phase and downregulating genes associated with androgen response and ferroptosis-related metabolic pathways. This study identifies TEAD4 as a master architect of the epigenetic and transcriptional reprogramming required for the acquisition of therapy resistance in CRPC.

In summary, these findings elucidate the multifaceted role of TEAD4 as a critical driver of therapeutic resistance in prostate cancer, establishing it as a high-priority candidate for therapeutic intervention. Pharmacologically targeting TEAD4 and its regulatory networks offers a viable strategy to circumvent epigenetic plasticity and treatment bypass. Such approaches may refine current treatment paradigms and significantly improve clinical outcomes for patients with CRPC.

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

Project No.: NHRI-EX115-11308BC
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, survival, and differentiation, and its dysregulation contributes to oncogenesis and a wide range of human diseases. Although RTK inhibitors (RTKi) have transformed targeted cancer therapy, their clinical efficacy is often limited by acquired resistance, pathway rewiring, and off-target effects.

To address these limitations, we are developing new strategies to modulate RTK signaling through tyrosine phosphatase-based mechanisms. Here, we report recent progress in two complementary directions: the development of a biologic PhosTAC (phosphorylation targeting chimera) format, termed togoPhosTAC via recruiting a tyrosine phosphatase PTPN2, and the discovery of a small-molecule PTPN2 inhibitor/degrader. The togoPhosTAC system uses a lipid-based nanoparticle delivery approach to encapsulate and co-deliver a pre-formed PhosTAC–phosphatase complex. Using recombinant PTPN2, we achieved rapid and effective EGFR dephosphorylation within 2 hours across multiple cell lines, including lung cancer cells. This targeted dephosphorylation also suppressed downstream signaling events, including phosphorylation of GAB1, SHC, and AKT, supporting the potential of phosphatase recruitment as an alternative strategy to directly modulate oncogenic RTK signaling.

In parallel, we performed a small-molecule screen and identified modulators of PTPN2. We identified six candidate inhibitors, among which compound I2 showed the strongest activity. I2 inhibited PTPN2 *in vitro* with an IC_{50} of approximately 0.26 μM, while showing substantially weaker inhibition of the related tyrosine phosphatases. Mechanistic studies further suggest that I2 covalently engages the catalytic site of PTPN2, with LC–MS/MS analysis supporting modification at Cys216. In cells, I2 induced rapid degradation of PTPN1/2 in multiple cancer cell lines, including Jurkat cells, with a DC_{50} of approximately 250 nM after 3 hours. Functionally, I2 enhanced STAT1 phosphorylation following IFN-γ stimulation, consistent with inhibition or depletion of PTPN2 activity and similar to the cellular effects of known PTPN2 inhibitors such as AC484.

Together, these findings establish a dual strategy for modulating PTPN2-dependent signaling: biologic phosphatase delivery through togoPhosTAC for targeted RTK dephosphorylation, and small-molecule intervention through I2-mediated PTPN2 inhibition and degradation. Ongoing efforts include structural characterization of PTPN2–I2 engagement, structure–activity relationship optimization, and expanded cellular studies to evaluate the therapeutic potential of PTPN2 modulation in RTK-driven cancer and immune signaling contexts.

Title of Project: Nanoparticle Delivery Systems to Target and Reprogram Tumor-Associated Macrophages for Cancer Immunotherapy

Project No.: NHRI-EX115-11401BI
P.I.: Yunching Chen/陳韻晶
NHRI Researcher: Shu-Yi Lin/林淑宜
Key Professional Personnel: Hsin-Mei Lee/李欣玫, Sheng-Liang Cheng/鄭聖良, Chung-Pin Li/李重賓
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Pancreatic ductal adenocarcinoma (PDAC) remains poorly responsive to immunotherapy because dense desmoplasia, abnormal vasculature, and immunosuppressive tumor-associated macrophages (TAMs) limit therapeutic delivery and effector-cell infiltration. We developed STING-Activating Macrophage Particles (STAMP), a macrophage-directed cGAMP nanotherapeutic designed to activate STING signaling selectively within TAMs and remodel the pancreatic tumor microenvironment. STAMP efficiently delivered cGAMP to M2-like macrophages, crossed tumor-associated vascular and stromal barriers, and penetrated PDAC spheroids. *In vitro* and in orthotopic PDAC models, STAMP activated TBK1-IRF3 signaling, induced type I interferon and pro-inflammatory chemokine programs, and repolarized immunosuppressive macrophages toward an M1-like phenotype with enhanced phagocytosis. Bulk and single-cell transcriptomic analyses further revealed activation of innate and adaptive immune pathways, NK-cell cytotoxic programs, and immune-organizing signatures consistent with tertiary lymphoid structure initiation. Therapeutically, STAMP suppressed primary tumor growth and reduced hepatic metastatic burden. It also enhanced the effects of gemcitabine and anti-PD-1 therapy, with the anti-PD-1 combination promoting stronger T-cell activation and prolonged survival. These findings support STAMP as a translational macrophage-directed immunoadjuvant platform for overcoming microenvironment-driven resistance in pancreatic cancer.

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

Project No.: NHRI-EX115-11318BI
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)

Acalabrutinib (ACA) is a clinically approved covalent Bruton's tyrosine kinase (BTK) inhibitor for B-cell malignancies. Here, we show that its anti-metastatic activity extends beyond canonical BTK inhibition through therapeutically beneficial polypharmacology. Using an unbiased chemical proteomic platform, we identified a novel ACA-binding protein 1, termed ABP-1, which is an actin-bundling protein that regulates cytoskeletal remodeling and cell motility, as a previously unrecognized covalent target of acalabrutinib. Acalabrutinib covalently modified the redox-sensitive cysteine residue of ABP-1, thereby disrupting actin bundling, abolishing filopodia and lamellipodia formation, and suppressing tumour cell invasion without substantial cytotoxicity. Functional studies established ABP-1 as the key mediator of this response, while the cysteine mutation abolished both ABP-1-driven metastasis and acalabrutinib sensitivity *in vivo*. In orthotopic prostate cancer models, acalabrutinib markedly suppressed systemic dissemination despite only modest effects on primary tumour growth. Clinical transcriptomic analyses further demonstrated that tumours with concurrent BTK and ABP-1 activation were associated with aggressive disease and metastatic signatures. Collectively, our findings identify ABP-1 as a previously unrecognized covalent target of acalabrutinib, redefine its mechanism of action beyond canonical BTK inhibition, and establish therapeutically beneficial polypharmacology as a strategy for targeting metastatic progression and expanding the clinical utility of covalent targeted therapies.

Title of Project: Evaluation of Drug Response Using Patient-Derived Tumor-Microenvironment-on-Chip for Breast Cancer

Project No.: NHRI-EX115-11319BI
P.I.: Jen-Huang Huang/黃振煌
NHRI Researcher: Hsin-Ling Hsu/徐欣伶
Key Professional Personnel: Chiao-Min Lin/林巧旻
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Cancer immunotherapy has transformed cancer treatment, particularly through the clinical success of immune checkpoint inhibitors and combination regimens. However, predicting which patients will benefit from immunotherapy remains challenging due to tumor heterogeneity, complex tumor–immune interactions, and the limited predictive power of current biomarkers such as PD-L1 expression. Conventional preclinical models, including two-dimensional cultures, organoids, and animal models, often fail to simultaneously provide human relevance, immune microenvironmental complexity, reproducibility, and sufficient throughput for practical therapeutic screening. To address these limitations, we developed a high-throughput humanized Tumor-Microenvironment-on-Chip (TMoC) platform for immunotherapy evaluation. Building on our previous TMoC design, the platform incorporates dynamic microfluidic perfusion to generate physiologically relevant gradients of oxygen, nutrients, and therapeutic agents, while enabling spatially resolved analysis of tumor responses. To improve scalability, a central pump-driven membrane pumping strategy was integrated into a modular automated system, allowing multiple culture units to be operated with improved consistency and reduced dependence on individual mechanical pumps. This platform is designed to bridge patient-derived organoid (PDO), patient-derived xenograft organoid (PDXO), and tumor-on-chip technologies. By incorporating tumor cells or patient-derived tumor models together with human peripheral blood mononuclear cells, the system allows the reconstruction of a humanized tumor immune microenvironment under dynamic circulation conditions. The platform enables evaluation of chemotherapy, targeted therapy, immune checkpoint blockade, and combination treatment strategies, while supporting analysis of patient-specific heterogeneity and tumor–immune interactions. Through systematic validation of platform stability, inter-unit reproducibility, tumor growth, immune cell incorporation, and drug response profiles, this study establishes a practical high-throughput TMoC approach for immunotherapy testing. The platform may provide a clinically relevant experimental tool to support therapeutic selection, reduce trial-and-error treatment strategies, and accelerate the development of next-generation precision immuno-oncology approaches.

Keywords: tumor-microenvironment-on-chip, immunotherapy, patient-derived organoids, humanized immune microenvironment, drug screening, precision oncology

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

Project No.: NHRI-EX115-11320BI
P.I.: Tzong-Yi Lee/李宗夷
Key Professional Personnel: Yann-Jen Ho/何彥禛, Chih-Hung Chung/鍾志宏, You Sheng Paik 裴友勝, Muh-Hwa Yang/楊慕華
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Drug response models trained on cancer cell lines often achieve high predictive accuracy in preclinical settings but fail to generalize to clinical cohorts due to substantial biological domain shifts and the limited availability of patient samples. To address this challenge, we present a kinase signaling-guided multi-omics and domain-adaptive framework that integrates prior biological knowledge with evolutionary learning to identify robust biomarkers associated with therapeutic response across heterogeneous domains. By leveraging kinase-centered regulatory networks and multi-omics features, the framework prioritizes biologically stable response-associated signatures while minimizing domain-specific variation between preclinical models and patient cohorts. Applied to cetuximab response prediction in head and neck squamous cell carcinoma, the framework identifies a six-gene signature (EGFR, MTOR, MYO1B, ANXA3, TGFB1, and CDKN2C) that demonstrates reproducible predictive performance across domains, achieving an AUC of 0.716 in clinical patient cohorts and 0.950 in an independent patient-derived xenograft (PDX) cohort (GSE183881). Functional analyses reveal coordinated dysregulation of EGFR signaling, kinase-mediated cell-cycle regulation, and therapy-induced stress response, providing mechanistic insights into cetuximab resistance and supporting biologically informed patient stratification. Notably, the identified signature also exhibits predictive relevance for docetaxel and afatinib response in independent preclinical datasets, suggesting broader applicability across targeted therapies. Collectively, these findings establish a kinase signaling-guided, multi-omics, and domain-adaptive framework for translating drug response biomarkers from preclinical models to clinical oncology and provide a generalizable strategy for pan-cancer drug resistance prediction.

Title of Project: Functional Study of DUSP2-regulated CARM1 in Colon Cancer Progression
Project No.: NHRI-EX115-11321BI
P.I.: Shaw-Jenq Sean Tsai/蔡少正
Key Professional Personnel: Jhao-Lin Fu/傅兆麟, Shaw-Jenq Tsai/蔡少正
Affiliation/Institution: National Cheng Kung University, National Chung Cheng University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Hypoxia is an inevitable stress in solid tumors and has been linked to promote drug resistance and cancer malignancy. However, the underlining mechanisms remain incompletely characterized despite numerous efforts in the past three decades. Herein, we report that hypoxic stress causes transcriptional upregulation of coactivator-associated arginine methyltransferase-1 (CARM1), which regulates critical pathological processes to drive cancer malignancy in colorectal cancer (CRC). Single cell sequencing analysis and immunohistochemical staining of clinical samples showed that CARM1 is markedly upregulated in CRC samples and is negatively associated with disease-free survival. Overexpression of CARM1 results in increasing levels of asymmetric histone H3 arginine 17 dimethylation (H3R17me2a) and asymmetric dimethylarginine (ADMA), which facilitate the expression of genes associated with cell cycle regulation, anchorage independent growth, and epithelial-mesenchymal transition. Furthermore, CARM1 dependent H3R17me2a promotes the expression of an RNA/DNA binding protein, FUS, which facilitates DNA repair and contributes to oxaliplatin resistance. Colon cancer patients with high levels of CARM1 and FUS exert the worst treatment efficacy and overall survival. Genetic or pharmacological disruption of CARM1 function abrogated hypoxia-induced H3R17me2a deposition, attenuated migratory and clonogenic capacities, and reduced oxaliplatin resistance. Consistent with these *in vitro* findings, CARM1 knockout orthotopic xenografts reduced primary tumor burden, increased sensibility to oxaliplatin, and abrogated metastasis. Collectively, these findings position CARM1 as a central integrator of hypoxic signaling and chemoresistance in CRC and provide a tractable therapeutic vulnerability. Targeting CARM1 may provide a rational precision-medicine strategy for the management of hypoxia-driven malignancy.

Title of Project: Deciphering the Mechanistic Link Between PCNA Tyrosine Phosphorylation and Anti-tumor Immunity: Implications for Immuno-oncology Therapy
Project No.: NHRI-EX115-11317BI
P.I.: Shao-Chun Wang/王紹椿
Affiliation/Institution: China Medical University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

USP5 suppresses MRE11 endonuclease function to facilitate tumor immune escape

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Replication stress is a hallmark of cancer that generates abnormal cytosolic DNA, thereby activating intrinsic immune pathways that constrain tumor growth. To survive, malignant cells must counteract these immune surveillance mechanisms, yet the underlying regulatory processes remain incompletely understood. The MRE11 nuclease plays a dual role in maintaining genome stability and processing stalled replication forks, where its endonuclease activity produces single-stranded DNA (ssDNA) capable of activating the cGAS-STING axis to induce anti-tumor immunity. In this study, we uncover a ubiquitin-dependent mechanism that connects DNA replication stress to immune evasion. Loss of tyrosine 211 phosphorylation on PCNA (pY211-PCNA) induces endogenous replication stress and promotes site-specific polyubiquitination of MRE11. This modification enhances MRE11 endonuclease activity, resulting in cytosolic ssDNA accumulation, activation of innate immune signaling, and increased susceptibility to natural killer (NK) cell-mediated cytotoxicity. Conversely, in cells expressing pY211-PCNA, the deubiquitinase USP5 is recruited to replication forks, where it removes ubiquitin from MRE11, thereby attenuating its endonuclease activity and suppressing cytosolic ssDNA formation and immune activation. Clinically, elevated USP5 expression correlates with tumor metastasis and poor prognosis in breast cancer. Genetic ablation or pharmacologic inhibition of USP5 restores MRE11-dependent ssDNA production, promotes NK cell infiltration, and suppresses tumor growth in immune-competent but not immune-deficient mouse models. An unbiased drug screen identified two FDA-approved compounds as potent USP5 inhibitors, which mimic USP5 depletion by enhancing cytosolic ssDNA accumulation, triggering NK- and PBMC-mediated killing of patient-derived tumor organoids (PDTOs), and suppressing tumor growth in syngeneic mouse models. These results identify USP5 as a critical negative regulator of MRE11-driven immunogenic DNA processing and reveal a therapeutic strategy to potentiate anti-tumor immunity through targeted USP5 inhibition.

Title of Project: Reprogramming the Metabolism, Polarization and Function of Tumor-associated Macrophages by E3 Ubiquitin Ligases

Project No.: NHRI-EX115-11402BI

P.I.: Chun-Jung Ko/柯俊榮

Key Professional Personnel: Meng-Yun Lin/林孟筠, Pei-Hsin Wang/王珮鑫

Affiliation/Institution: National Taiwan University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

Tumor-associated macrophages (TAMs) are a dominant immune population within the tumor microenvironment (TME) and play pivotal roles in cancer progression through their functional plasticity. During tumor progression, TAMs are frequently reprogrammed toward a tumor-promoting phenotype that supports tumor growth and suppresses antitumor immunity. However, the molecular mechanisms governing this process remain incompletely understood. Here, we identify the E3 ubiquitin ligase, inducible degrader of the low-density lipoprotein receptor (IDOL), as an unrecognized regulator of TAM plasticity and tumor immunity in pancreatic ductal adenocarcinoma (PDAC).

Analysis of publicly available human PDAC single-cell RNA-sequencing datasets revealed that IDOL expression was significantly lower in tumor-promoting TAMs than in TAMs with more inflammatory or antitumor-associated features. Consistently, TAMs isolated from a syngeneic KPC pancreatic tumor model also exhibited markedly reduced IDOL expression. IDOL deficiency accelerated tumor growth in KPC tumor models and increased the accumulation of TAMs, particularly $CD206^+$ TAMs. Mechanistically, we found that IL-4 suppressed IDOL expression in macrophages through an IRS1/2 signaling-dependent pathway. Under tumor-derived environmental cues, IDOL-deficient bone marrow-derived macrophages (BMDM) and immortalized BMDMs acquired a tumor-promoting phenotype, characterized by increased CD206 and arginase-1 expression, together with reduced inflammatory macrophage features, including decreased M1-associated cytokines and iNOS expression. Functionally, conditioned medium from IDOL-deficient TAM-like BMDMs significantly promoted KPC cell proliferation, while direct co-culture with IDOL-deficient BMDMs impaired $CD8^+$ T-cell effector function, as indicated by reduced IFN- and granzyme B production.

Collectively, these findings suggest that IDOL constrains tumor-promoting polarization and limits TAM-mediated tumor growth and T-cell suppression in PDAC. Our study identifies IDOL as a potential regulatory node that may be exploited to modulate the immunosuppressive tumor microenvironment in pancreatic cancer.

Title of Project: Direct Transfer of Lipids from the Tumor-associated Macrophages to Tumor Cells in the Progression of Clear-cell Renal Cell Carcinoma
Project No.: NHRI-EX115-11403BI
P.I.: Tien Hsu/徐沺
Key Professional Personnel: Kuo-How Huang/黃國皓, Wen-Lung Ma/馬文隆
Affiliation/Institution: China Medical University
Entire Project Period: From 2025 to 2029 (Total: 5 years)

APOE-Mediated Immune-Metabolic Reprogramming of Macrophages Drives Lipid Delivery to Tumor Cells in Clear-Cell Renal Cell Carcinoma

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Clear-cell renal cell carcinoma (ccRCC) is defined by cancer cells with lipid-filled cytoplasm that appears "clear" in tissue preparations**;** however, the origin of these lipids and their role in tumor progression remain unclear. Notably, cultured ccRCC cells rarely exhibit the clear-cell phenotype *in vitro*, suggesting that lipid accumulation in ccRCC is not cell-autonomous. Here we show that tumor-associated macrophages (TAMs) undergo immunometabolic reprogramming and serve as major suppliers of lipids for ccRCC cells. Upon activation by the tumor suppressor gene *VHL*-deficient kidney tubule cells, TAMs acquire adipogenic and cholesterol metabolic signatures, accumulate lipids, and differentiated into lipid-laden macrophages (LLMs) via a TGF-β-APOE-dependent pathway. LLMs then transfer lipids directly to tumor cells through tunneling nanotubes (TNTs). Lipidomic analyses revealed that LLMs and recipient tumor cells share nearly identical lipid profiles enriched in cholesterol and phosphatidates, but not triglycerides. In patient cohorts, elevated APOE expression levels in macrophages (MΦs) correlated with advanced disease stages. *In vivo*, disruption of MΦ**-**specific APOE expression abrogated the clear-cell phenotype, reduced tumor growth, and suppressed metastasis in autochthonous and orthotopic xenograft ccRCC models. These findings identify a previously unrecognized MΦ-tumor crosstalk in which reprogrammed TAMs supply lipids to tumor cells, driving the clear-cell phenotype and disease progression. Targeting the TGF-β-APOE axis or TNT-mediated lipid transfer represents a potential therapeutic strategy. More broadly, this work supports a "metabolic checkpoint" paradigm, revealing a therapeutically amenable vulnerability in ccRCC.

Title of Project: Development of Protein Kinase C Delta (PKCδ) Target Therapy for EGFR TKI-resistant Lung Cancer

Project No.: NHRI-EX115-11413BI
P.I.: Pei-Chih Lee/李培志
Key Professional Personnel: Mien-Chie Hung/洪明奇, Yi-Wen Chen/陳怡文
Affiliation/Institution: China Medical University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) remains the primary challenge in treating EGFR-mutant non-small cell lung cancer (NSCLC). We have previously identified nuclear PKCδ (nPKCδ) as a critical, convergent signaling node in approximately 40% of clinical TKI-resistant tumors. Given that existing pan-PKC inhibitors lack the specificity and efficacy required for clinical application, we employed a drug-repurposing strategy to identify a more precise therapeutic agent.

In this study, we identified nintedanib (Nin) as a potent and selective inhibitor of nPKCδ. Mechanistic investigations reveal that Nin promotes the proteasome-dependent degradation of nuclear PKCδ while sparing its cytoplasmic pool and other PKC isoforms, thereby minimizing the off-target toxicities historically associated with broad-spectrum PKC inhibition.

Using a robust panel of TKI-resistant cell lines and acquired resistant clones, we demonstrated that Nin effectively disrupts core survival signaling pathways, including S6K, ERK, and AKT. Nin exhibited strong synergistic effects when combined with first-generation (gefitinib, erlotinib) and third-generation (osimertinib) TKIs.

In vivo xenograft studies validated these findings, showing that Nin combined with osimertinib significantly delayed tumor progression, with some models exhibiting marked regression. While traditionally classified as an angiogenesis inhibitor, our data repurpose Nin as an effective nPKCδ inhibitor. Notably, this therapeutic efficacy was observed even in angiogenesis-independent tumor models, confirming that Nin reverses TKI resistance via nPKCδ modulation rather than solely through anti-angiogenic effects.

Collectively, our results establish Nin as a potent, clinically available agent that overcomes heterogeneous resistance mechanisms by targeting the nPKCδ-driven survival axis. These findings provide a strong biological rationale for clinical trials evaluating Nin-TKI combination therapies to improve outcomes in patients with TKI-resistant EGFR-mutant NSCLC.

Title of Project: Integrating Metabolic Gene Regulatory Network with Synthetic Gene Circuit for Neuroendocrine Prostate Cancer Immunotherapy

Project No.: NHRI-EX115-11414BI

P.I.: Yen-Nien Liu/劉晏年

Key Professional Personnel: Yen-Nien Liu/劉晏年

Affiliation/Institution: Taipei Medical University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

Neuroendocrine prostate cancer (NEPC) is a lethal, treatment-resistant subtype arising under androgen deprivation therapy (ADT), characterized by an immunosuppressive tumor microenvironment and poor response to existing treatments. Therapy-induced metabolic reprogramming is increasingly recognized as a driver of lineage plasticity and immune evasion in castration-resistant prostate cancer (CRPC), yet the molecular programs coordinating these processes remain poorly defined. In this study, we identify a metabolic-glycosylation regulatory axis that is progressively upregulated from CRPC to NEPC, as demonstrated by single-cell transcriptomic profiling of patient-derived specimens and validated in paired pre- and post-ADT clinical biopsies. We show that ADT coordinately induces this axis alongside neuroendocrine differentiation and stemness programs while suppressing androgen receptor signaling. Mechanistic studies establish that a nuclear metabolic enzyme cooperates with a neuroendocrine master transcription factor to directly activate a glycosyltransferase target, linking lineage plasticity to post-translational immune checkpoint regulation. The induced glycosyltransferase stabilizes PD-L1 surface expression through N-glycosylation, enabling tumor cells to suppress T cell and macrophage anti-tumor activity. Genetic ablation of this glycosyltransferase in a syngeneic prostate cancer model reduced tumor growth and reprogrammed the tumor microenvironment toward anti-tumor immunity. High expression of this axis associated with shorter overall survival in a large clinical cohort. These findings define a previously unrecognized mechanistic nexus between metabolic adaptation, neuroendocrine lineage plasticity, and glycosylation-dependent immune evasion in treatment-resistant prostate cancer, with implications for developing targeted combination immunotherapeutic strategies.

Title of Project: Deciphering the Differential Roles of YAP and TAZ in Tumor Immunity
Project No.: NHRI-EX115-11415BC
P.I.: Wei-Chien Yuan/袁維謙
Affiliation/Institution: National Yang Ming Chiao Tung University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

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The Hippo pathway effectors YAP and TAZ are widely regarded as functionally redundant drivers of tissue growth and cancer. Here, we challenge this paradigm and demonstrate that YAP and TAZ possess fundamentally distinct biological functions *in vivo*. Using CRISPR-engineered *Yap*^{Taz} knock-in mice, we show that TAZ cannot substitute for YAP during development, revealing an unexpected requirement for YAP-specific functions. Although TAZ induces stronger acute proliferative responses and promotes more aggressive tumor growth in immunodeficient hosts, TAZ-driven tumors are selectively eliminated in immunocompetent mice, exposing a previously unrecognized susceptibility to immune surveillance. By contrast, YAP enables durable tumor progression by actively suppressing anti-tumor immunity and remodeling the tumor microenvironment. Consistently, CyTOF profiling reveals a profound enrichment of immunosuppressive immune populations in YAP-driven tumors but not in TAZ-driven tumors. Mechanistically, TAZ displays higher TEAD binding affinity than YAP, with overlapping yet distinct transcriptional programs between these paralogs. Together, our findings redefine the relationship between YAP and TAZ, establish YAP as a dominant regulator of immune suppression and tumor fitness, and provide a conceptual framework for the selective targeting of YAP-driven malignancies.

Title of Project: Old Trick in the New Era:a Mechanistic Study of Anti-estrogen to Optimize Immunotherapy in Hormone Receptor Positive Breast Cancer

Project No.: NHRI-EX115-11416BC
P.I.: I-Chun Chen/陳怡君
Affiliation/Institution: National Taiwan University Cancer Center
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Background

Estrogen is an important molecule differentiated women between premenopausal and postmenopausal biologic status. The role of estrogen in breast cancer is well characterized. As for the immune system, estrogen was known to shift the balance between immunosuppressive and immunoactive status. Our study aims to investigate the role of estrogen in the modulation of immunotherapy in breast cancer patients.

Miletones and findings

1. We have published our manuscript, “Hormone therapy enhances anti-PD1 efficacy in premenopausal estrogen receptor-positive and HER2-negative advanced breast cancer. ” in the Cell Reports Medicine journal in 2025. We have demonstrated that adding hormone therapy to immunotherapy was much more effective than either treatment alone in ER positive metastatic breast cancer. In this study, blocking estrogen has turned immune cold into immune hot microenvironment in ER positive/ HER2 MBC.
2. In our preclinical model, we have compared pre-menopausal and post-menopausal levels of estrogen on the function of CD8+ T cells. We used charcoal treated medium to treat the CD8+ T cells and adding back premenopausal/ postmenopausal levels of estrogen. In this preclinical cell model, we have confirmed that using postmenopausal (low) estrogen will enhance oxygen consumption rate as compared to premenopausal (high) estrogen treated CD8+ T cells. We have also applied RNAseq analysis to compare the signaling pathway differences between CD8+ T cells treated with premenopausal and postmenopausal levels of estrogen.
3. In oure preclinical model, we have also generated ESR1 knockout CD8+ T cells from R26R Cas9 MPH mouse. Using genetic ablatino of ESR1, we have demonstrated that blocking ESR1 in CD8+ T cells will attenuate the oxygen consumption rate increase when the CD8+ T cells are treated with postmenopausal levels of estrogen.

Future work

1. We will compare the effect of genetic ablation and different physiological levels of estrogen on the regulation of CD8+ T cell function and its metabolic impact.
2. We will investigate the mechanisms by which estrogen can influence CD8+ T cell metabolism and therefore regulating their function.

Title of Project: The Mechanism of CDK5-mediated Resistance to PARP Inhibitors and the Development of Combination Therapy and Biomarkers to Overcome It

Project No.: NHRI-EX115-11425BI

P.I.: Hirohito Yamaguchi/山口浩史

Key Professional Personnel: Hirohito Yamaguchi/山口浩史, Yu-Jung Che/陳又榕, Mien-Chie Hung/洪明奇, Tewodros Shegute, Yu-Chun Hsiao/蕭宇君

Affiliation/Institution: China Medical University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

Poly(ADP-ribose) polymerase inhibitors (PARPi) exert dramatic therapeutic effects on breast cancers with homologous recombination deficiency. However, overcoming acquired resistance remains an urgent challenge. Through the analysis of existing CRISPR screening and transcriptome datasets, we identified CDK5 as a novel target for enhancing PARPi sensitivity. CDK5 and its activator CDK5R1 were overexpressed in breast cancer tissues and correlated with poor prognosis. Furthermore, CDK5 activation was observed in PARPi-resistant cells. This study aimed to elucidate the molecular mechanisms by which targeting CDK5 overcomes PARPi resistance.

In several breast cancer cell lines, the combination of a CDK5 inhibitor and a PARPi induced potent synergistic effect (suppression of colony formation). Knockdown of CDK5 enhanced PARPi sensitivity, whereas its overexpression induced resistance. Moreover, in a breast cancer cell xenograft mouse model, the CDK5 inhibitor significantly potentiated the tumor-growth inhibitory effect of the PARPi.

Through mechanistic analysis, we revealed that CDK5 inhibition significantly enhanced PARPi-induced DNA double-strand breaks and PARP trapping on DNA. Furthermore, we identified STUB1 as a ubiquitin E3 ligase that is overexpressed in breast cancer and interacts with both CDK5 and PARP1. We discovered that CDK5 phosphorylates STUB1 at serine 19 (S19), thereby suppressing PARP trapping via STUB1-mediated ubiquitination of PARP1. Indeed, cells expressing a non-phosphorylatable mutant (S19A) exhibited decreased PARP ubiquitination alongside markedly enhanced PARPi-induced trapping and DNA damage compared to wild-type cells. Conversely, a phosphomimetic mutant (S19D) showed the opposite effects.

In conclusion, CDK5 regulates PARP1 ubiquitination and trapping via the phosphorylation of STUB1 at S19, thereby determining PARPi sensitivity. These findings demonstrate that a combination therapy of a CDK5 inhibitor and a PARPi would be a promising therapeutic strategy to overcome PARPi-resistance in breast cancer.

Title of Project: Deciphering EBV Lytic Gene Products-induced Cellular Compartment Reorganization to Combat EBV Associated Diseases

Project No.: NHRI-EX115-11426BI
P.I.: Mei-Ru Chen/陳美如
Key Professional Personnel: Yu-Hsuan Liang/梁妤暄
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Importin 5 Is Required for BFRF1-induced Nuclear Membrane Remodeling and Efficient Replication of Epstein-Barr Virus

Epstein-Barr virus (EBV) nucleocapsids exit the nucleus through a coordinated process orchestrated by the viral nuclear egress complex (NEC), which is composed of the viral proteins BFRF1 and BFLF2. Our previous work established that BFRF1 recruits the host adaptor protein Alix and recruit the ESCRT machinery to facilitate nuclear membrane remodeling. Although a potential interaction between BFRF1 and Importin 5 (IPO5) has been previously suggested, its precise mechanism and functional significance remain poorly understood. Here, we investigated the functional role of the nuclear transport receptor IPO5 in EBV nuclear egress. Indirect immunofluorescence assays demonstrated that BFRF1 induces the redistribution of IPO5 to the nuclear periphery, suggesting a potential functional association. To map the interacting domains, GST pull-down assays, identified a direct interaction between the late budding-like domain 1 (LD1, a.a. 8–65) of BFRF1 and the C-terminal region of IPO5. Functionally, knockdown of IPO5 markedly attenuated BFRF1-induced cytoplasmic distribution of nuclear envelope-derived vesicles. Furthermore, during Rta-mediated viral reactivation, depletion of IPO5 significantly impaired virion release in TW01-EBV cells. Loss of IPO5 also perturbed the spatial organization of Alix within the viral assembly compartment (vAC), indicating a functional interaction between IPO5 and ESCRT-associated factors. Confocal microscopy revealed that deletion of the EBV-specific region of BFRF1 (a.a. 180–314) disrupts its proper localization at the nuclear envelope, leading to endoplasmic reticulum (ER) reorganization and the formation of aberrant ER-derived vesicles. Furthermore, the BFRF1-IPO5 colocalization is dependent on the presence of Alix. GST pull-down assays confirmed a dose-dependent relationship among BFRF1, Alix, and IPO5, suggesting they may function as a ternary complex. Taken together, these findings identify IPO5 as a novel regulator of BFRF1 activity and suggest that IPO5 facilitates EBV nuclear egress and virion maturation, potentially by modulating Alix trafficking and ESCRT engagement.

Title of Project: Single-cell Investigation of P53-induced DNA Damage for the Control of Non-genetic Heterogeneity in Cancer Cells

Project No.: NHRI-EX115-11427BI
P.I.: Sheng-Hong Chen/陳昇宏
Key Professional Personnel: Ann Mikaela Co, Feng-Shu Hsieh, Chia-Chou Wu, Yu-Hsiang Chen
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Genotoxic cancer therapy creates a fundamental paradox in tumour biology, namely that the same DNA damage responses that suppress tumour growth through cell death or senescence can also drive adaptive tumour evolution by promoting genomic instability. Tetraploidy, induced by genotoxic stress, is a critical intermediate state that can either reinforce tumour suppression through durable arrest or serve as a substrate for aneuploidy, diversification, and therapy resistance. Yet, how newly formed tetraploid cells are directed toward these divergent fates remains unknown. Given that p53 lies at the intersection of genotoxic stress responses and tetraploidization, p53 signaling is potentially a critical determinant of this paradoxical response. We sought to determine how p53-dependent control of mitotic bypass interfaces with the endoreplication versus senescence fate decision of tetraploid cells. We used the single cell imaging approach to monitor and quantify the dynamics of p53 and cell cycle transitions following treatment with a non-genotoxic inducer of p53 (Nutlin-3a) and conventional chemotherapy drugs (etoposide, teniposide, 5-fluorouracil). We further elucidated the molecular mechanisms involved using inducible constructs, endogenous p21- and CDK2 activity reporters, immunofluorescence staining, and DNA fiber assay. Characterization of cellular fate was done by coupling live cell imaging of H2B reporters (to characterize mitotic aberrations) with β-gal staining (to mark entry into senescence) after Nutlin-3a or chemotherapy treatment. We found that p53 dynamics govern a bifurcation in cell-cycle exit, generating tetraploid cells with divergent evolutionary potential. The p53 dynamics, encompassing the timing, duration and intensity of activation relative to S phase, regulate engagement of a p21–CDK2 regulatory switch. When engaged during S phase, this switch suppresses CDK2 activity and drives premature transitioning to a G0-like biochemical state that bypasses G2 and mitosis. This aberrant cell cycle exit permits DNA re-replication and DNA damage accumulation, giving rise to a pseudo-G0 (Ψ-G0) state predisposed to senescence and cell death. In contrast, engagement after S phase permits mitotic bypass following G2, generating proliferative 4N-G1 tetraploid cells that are prone to mitotic aberrations, aneuploidy and genome diversification, thereby creating a substrate for tumour evolution. Our findings establish a central role for p53 dynamics in shaping tetraploid cell fate through bifurcating cell-cycle exit trajectories, providing a conceptual framework for understanding how genome doubling influences tumour evolution.

Title of Project: Functional Role of *O*-GlcNAcylation in B1 Cells and Its Involvement in Cancer Progression

Project No.: NHRI-EX115-11428BI
P.I.: Kuo-I Lin/林國儀
Key Professional Personnel: Kuo-I Lin/林國儀
Affiliation/Institution: Academia Sinica
Entire Project Period: From 2025 to 2027 (Total: 3 years)

O-GlcNAcylation, a key type of intracellular glycosylation, is catalyzed by *O*-GlcNAc transferase (OGT), which transfers the GlcNAc moiety from UDP-GlcNAc to the serine/threonine residues of cytoplasmic and nuclear proteins. We previously demonstrated that mature B-cell survival in the bone marrow and activation in the spleen depend on *O*-GlcNAcylation downstream of B-cell activating factor (BAFF) and B-cell receptor (BCR) signaling. B-1 cells develop in the fetal liver, and the majority migrate to and reside within the peritoneal and pleural cavities. Upon encountering pathogen-associated molecular patterns, B-1 cells migrate to the spleen, where they generate natural antibodies and cytokines for rapid pathogen defense. Given that B-1 cells exhibit a distinct response to BCR ligation and do not require BAFF signaling for survival, we sought to determine whether they depend on *O*-GlcNAcylation for homeostasis. Utilizing B-cell-specific *Ogt*-knockout (B-KO) mice, we found that *Ogt* deficiency significantly reduced the B-1 cell population in the body cavities; however, it did not impair their survival or proliferation. Transcriptomic analysis of splenic B-1 cells revealed that genes involved in cell migration and adhesion are regulated by *O*-GlcNAcylation. Specifically, the surface expression of several integrins was decreased upon *Ogt* deletion. Indeed, adoptive transfer, transwell migration, and adhesion assays consistently demonstrated that the loss of *O*-GlcNAcylation impairs B-1 cell migratory capacity. By analyzing the promoter sequences of differentially expressed genes (DEGs), we identified several transcription factors (TFs), including Runx3, that undergo *O*-GlcNAcylation in B cells. Mass spectrometry and Western blotting identified multiple conserved mammalian *O*-GlcNAcylation sites on Runx3. Mutating a key *O*-GlcNAc site increased Runx3 stability but attenuated the changes in BCL1 cell-surface integrin expression typically induced by Runx3 overexpression. Taken together, our findings indicate that *O*-GlcNAcylation maintains B-1 cell homeostasis by facilitating their migration into the body cavities, a process potentially mediated by Runx3-dependent modulation of surface integrin expression. Future studies will focus on the precise mechanisms by which *O*-GlcNAcylation regulates Runx3.

Title of Project: Cancer-stromal Interaction Through Soluble Factor and Transcription Networks in Pancreatic Cancer

Project No.: NHRI-EX115-11501BI
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 2026 to 2028 (Total: 3 years)

Chitinase-3-like-protein 1 (CHI3L1), a low-abundance protein in normal tissues, is markedly upregulated in the pancreatic tumor microenvironment (TME), where it promotes fibrosis and immune evasion. Spatial transcriptomics revealed enrichment of CHI3L1 at tumor-stroma interfaces, suggesting that cell-cell interactions regulate CHI3L1 expression. We employed 2D and 3D multicellular culture models comprising pancreatic cancer cells, macrophages, and pancreatic stellate cells (PSCs) to recapitulate TME-mediated CHI3L1 induction. Mechanistic insights were gained through secretome profiling, chromatin immunoprecipitation (ChIP), and methylation-specific PCR. The therapeutic potential of targeting identified axes was evaluated in an orthotopic PDAC mouse model. We identified CCL2, CXCL10, and SPARC as key secreted mediators during tumor-stroma crosstalk that cooperatively induced CHI3L1 expression in cancer cells via NF-κB and STAT3 activation. Specifically, inflammatory cytokines within the TME recruited macrophages to induce CCL2, which, in concert with PSCs, enhances CXCL10 and SPARC secretion. Mechanistically, NF-κB directly bound the *CHI3L1* promoter, while STAT3 reduced DNA methyltransferase 1 levels, leading to promoter hypomethylation and epigenetic activation of CHI3L1. Clinically, high CHI3L1 expression correlated with the upregulated stromal CCL2, CXCL10, and SPARC levels, and poor prognosis. *In vivo*, dual blockade of the CCL2/CCR2 axis and CHI3L1 reduced tumor growth and fibrosis and reversed immunosuppressive TME. Our findings reveal a TME-driven, stepwise regulatory network that orchestrates CHI3L1 expression in cancer via transcriptional and epigenetic reprogramming. These results suggest that disrupting the initiator CCL2/CCR2 axis, particularly when combined with CHI3L1 neutralization, represents a promising therapeutic strategy to reverse the immunosuppressive TME in PDAC.

Title of Project: An Innovative AI-driven Spatial Analysis Approach to Investigate the Microenvironment Heterogeneity of Betel Nut-induced Oral Squamous Cell Carcinoma and Immunotherapy Efficacy

Project No.: NHRI-EX115-11524BI
P.I.: Shu-Han Yu/游舒涵
Key Professional Personnel: Shu-Han Yu/游舒涵, Huai-Cheng Huang/黃懷正
Affiliation/Institution: National Taiwan University

Background: Oral squamous cell carcinoma (OSCC) is the most common malignancy of the head and neck region and poses a substantial health burden in populations where betel nut (BN) chewing is highly prevalent.

Purpose: Although BN exposure is a well-established etiological factor for OSCC, its impact on tumor biology and the tumor immune microenvironment (TIME) remains incompletely understood. Furthermore, it remains unclear whether PD-L1 serves as the primary immune checkpoint signature (ICS) modulated by BN consumption, and how such alterations dictate immunotherapy efficacy.

Study Design and Methods: In this study, we integrated a multi-omic approach combining WES, bulk RNA sequencing, and multiplex immunohistochemistry (mIHC) to delineate the ICS-patterns and immune landscapes of BN-associated OSCC. The study cohort included 40 patients divided equally based on BN exposure and clinical response. Specifically, the cohort included 20 BN-exposed patients and 20 non-exposed control patients from NTUH; within each of these two primary groups, 10 patients were classified as immunotherapy responders and 10 as non-responders.

Results: Our preliminary data demonstrate that BN-associated tumors exhibit enhanced IFNα/γ signaling and robust $CD8^+$ T cell infiltration, indicative of an immune-inflamed TIME. This inflamed state is accompanied by elevated *MYC* expression, aberrant lipid metabolism (characterized by reduced CD36 expression), and dense spatial macrophage clusters that physically encapsulate infiltrating $CD8^+$ T cells. Notably, high-*MYC* tumors exhibit markedly increased PD-L1 expression on both neoplastic cells and macrophages, accompanied by a phenotypic shift characterized by decreased M1 macrophages, increased M2 macrophages, and enhanced macrophage spatial clustering. Microenvironment topology analysis further revealed that exhausted $CD8^+$ T cells are preferentially localized adjacent to $PD\text{-}L1^+$ M2-like macrophages. Critically, this checkpoint-rich spatial architecture is associated with impaired T cell fitness: high-*MYC* tumors are predominantly enriched for terminally exhausted $CD8^+$ T cells, whereas low-*MYC* tumors retain a greater proportion of early, progenitor-like exhausted $CD8^+$ T cells.

Conclusions: Collectively, these findings suggest that BN-associated, *MYC*-high OSCC represents a paradoxically dysfunctional “hot” tumor state. Although characterized by robust immune activation and aberrant lipid metabolism, this state features accelerated M2-like macrophage polarization, elevated checkpoint expression, and increased spatial clustering. Importantly, these dense macrophage aggregates promote enhanced co-localization of exhausted $CD8^+$ T cells with M2-like TAMs, forming immune-evasive niches that drive terminal T cell exhaustion and immunotherapy resistance.

Title: Human Pan-Cancer Tumor–Sensory Neuron Co-culture Platform for Investigating Neuro-Cancer Interactions Using 3D Tumor Models and Microfluidics

P.I.: Chia-Hsien Hsu/許佳賢

Presenter: Preetismita Saikia/賽蓓思

Institute/Center: National Health Research Institutes

Background

Tumor innervation is an established hallmark driver of cancer progression across oral, breast, and lung cancers, with sensory nociceptors releasing neuropeptides and neurotrophins — including calcitonin gene-related peptide (CGRP), Substance P (SP), and brain-derived neurotrophic factor (BDNF) — that promote tumor proliferation, survival, and chemoresistance. However, which specific neuron-derived secreted factor most significantly drives pan-cancer tumor progression in compartmentalized human *in vitro* models remains poorly defined, representing a critical gap in translational cancer neuroscience.

Hypothesis

Sensory neurons promote pan-cancer progression through a broader secretory profile beyond known neuropeptides; identifying and blocking the dominant neuron-derived secreted factors will reveal a novel, therapeutically targetable neural dependency across diverse solid tumors.

Methods

Human SH-SY5Y neuroblastoma cells (ATCC CRL-2266) are differentiated into sensory-like neurons over 10 days using sequential retinoic acid (10 µM, Day 0) and BDNF (50 ng/mL, Day 3) treatment with progressive serum reduction. CAL 27 oral squamous cell carcinoma cells (ATCC CRL-2095) serve as the primary pan-cancer model — with planned extension to breast (MDA-MB-231, MCF-7) and lung (A549) cancer lines — grown as scaffold-free 3D tumor spheroids in ultra-low attachment (ULA) 96-well plates and monitored by brightfield imaging at Days 1, 3, and 7. Neuron conditioned media (NCM) is collected exclusively from differentiated SH-SY5Y neurons in the absence of tumor cells, ensuring all profiled secreted factors are strictly neuron-derived. NCM is applied to Day 7 tumor spheroids, with growth quantified by diameter and cross-sectional area over 72 hours. ELISA-based secretome profiling of NCM identifies dominant secreted neural factors, followed by targeted pharmacological blockade using clinically relevant inhibitors to establish causal neuro-tumor relationships.

Preliminary Results

Phase I validation confirmed reproducible CAL 27 spheroid formation across seeding densities of 1,000, 2,000, and 3,000 cells/well, with stable compact spheroids of approximately 235 µm at 2,000 cells/well by Day 7 — within the viable size range without significant necrotic core formation. SH-SY5Y differentiation produced extensive neurite outgrowth confirming a functional neural secretion source. NCM application experiments and ELISA-based secretome profiling are in progress. Subsequently, validated findings will be extended to breast and lung cancer lines to confirm pan-cancer applicability."

Significance

This study establishes a human, animal-free platform to systematically identify and block neuron-derived secretory factors driving pan-cancer progression. Validated findings will be integrated onto the lab's patented Microfluidic Hanging Drop (OST) co-culture device for compartmentalized neuro-tumor interaction studies, with a future roadmap incorporating patient-derived organoids (PDOs) and human iPSC-derived sensory neurons for translational, patient-specific neuro-oncology drug discovery.

Title of Project: Deep Learning-enhanced Ultra-low-count Tau PET Neuroimaging
Project No.: NHRI-EX115-11205EC
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)

Deep learning methods have enabled low-count PET enhancement to minimize radiation exposure while maintaining diagnostic image quality. However, traditional deterministic models inherently suffer from over-smoothing, and recent fast generative models, such as Consistency Models (CM), frequently exhibit peak signal attenuation in sparse, high-intensity lesions. Furthermore, existing models often prioritize visual realism over mathematical accuracy, leading to a "quantitative flaw" where structurally perfect images exhibit severe systematic bias in regional Standardized Uptake Value ratios (SUVr) . This study proposes using an Optimal-Transport Conditional Flow-Matching (OT-CFM) framework to enhance low-count Tau PET images, prioritizing both high-fidelity structural recovery and rigorous clinical quantification.

Forty-six participants, inclusive of individuals with Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, and healthy controls, were injected with the tau radiotracer [^{18}F]-APN-1607. A Dose Reduction Factor (DRF) of 6 was applied to generate 5-minute low-count PET inputs, paired with T1-weighted MRI structural priors. A 2.5D time-embedding U-Net was trained using the OT-CFM paradigm to construct straight, simulation-free probability paths between low-count noise and full-count target distributions. To address the "quantitative flaw" observed in traditional generative methods, our training objective was explicitly engineered to optimize for direct SUVr prediction, rather than raw intensity mapping.

Experimental results demonstrate that OT-CFM outperforms both the baseline low-count images and prior work's U-Net-based deterministic model (UNet3+) and Conditional Consistency Model (cCM) in global quality metrics, achieving enhanced structural similarity and peak signal-to-noise ratios. Visually, OT-CFM effectively recovers sharp, focal tau hotspots in critical AD-related regions, overcoming the over-smoothing artifacts and signal attenuation prevalent in baseline consistency models. Quantitative verification, utilizing intensity profiles, Full Width at Half Maximum (FWHM) analysis and Bland-Altman statistical plots, confirmed that OT-CFM restores boundary sharpness and peak SUVr values to levels consistent with full-count ground truth. Furthermore, OT-CFM demonstrated superior computational efficiency, requiring fewer function evaluations during inference than established CM or diffusion-based models. These findings reinforce the efficacy of OT-CFM as a fast, stable, and highly quantifiable solution.

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-EX115-11206EC
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)

Ultrasound Responsive Liquid Foam Overcomes Biological Barriers to Treat Advanced Intracavitary Metastasis

Metastatic dissemination within the pleural and peritoneal cavities represents a therapeutically challenging stage of advanced cancer, characterized by poor drug distribution, limited tumor penetration, and unsatisfactory treatment outcomes. Conventional locoregional therapies are frequently hindered by inadequate cavity-wide coverage and restricted intratumoral delivery, resulting in suboptimal therapeutic efficacy. Here, we developed Sonofoam, an injectable ultrasound-responsive foam platform engineered to achieve broad intracavitary distribution and locally controlled therapeutic activation. Upon extracorporeal ultrasound stimulation, microbubbles embedded within the foam undergo acoustic cavitation, generating localized mechanical forces that transiently enhance tumor permeability and facilitate deep intratumoral drug transport. *In vitro* studies demonstrated significantly enhanced cellular uptake and markedly improved cytotoxic efficacy following ultrasound activation. In metastatic mouse models, Sonofoam achieved substantially broader cavity distribution compared with conventional hydrogel formulations and significantly increased intratumoral penetration of therapeutic agents. Repeated treatment with cisplatin-loaded Sonofoam resulted in superior tumor suppression and prolonged survival compared with control treatments. Beyond enhancing drug delivery, ultrasound-activated Sonofoam remodeled the tumor immune microenvironment, reducing tumor proliferation while promoting increased infiltration of cytotoxic immune cells within tumor tissues. Notably, this therapeutic strategy achieved these benefits without detectable systemic toxicity. Collectively, these findings establish Sonofoam as a noninvasive and broadly applicable ultrasound-activated therapeutic platform capable of overcoming physical delivery barriers, enhancing local drug penetration, and potentiating antitumor immune responses for the treatment of advanced intracavitary metastatic disease.

Title of Project: Exploring the Neural Inhibition Hypothesis in Negative BOLD Phenomenon.
Project No.: NHRI-EX115-11322EI
P.I.: Jyh-Horng Chen/陳志宏
Key Professional Personnel: Jyh-Horng Chen/陳志宏
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Cross-state comparisons of BOLD amplitude are difficult to interpret when physiological conditions may alter vascular reactivity or neurovascular coupling. This study examined whether acute normobaric hypoxia changes load-dependent cortical BOLD modulation during working memory and whether the effect is confined to default mode network deactivation.

Forty-two healthy adults completed 0-back and 2-back tasks under normoxia (21% O_2) and hypoxia (12% O_2) in a fixed order.The primary contrast tested the oxygen-by-load interaction.

A cross-fitted, direction-aligned whole-cortex index showed that load-related responses shifted toward zero under hypoxia. The effect was robust in deactivated default-mode regions, including inferior parietal and posterior cingulate/precuneus parcels, but was not specific to the default mode network and did not differ detectably between activated and deactivated cortex.

More broadly, when physiological states may alter vascular reactivity or neurovascular coupling, the relationship between BOLD amplitude and underlying neural activity or vascular responses should not be assumed to remain constant across states. Without additional physiological or calibration measurements, BOLD amplitude should not be interpreted as a quantitative index of cross-state changes in neural activation or vascular responses.

The default mode network (DMN) is suppressed during cognitively demanding tasks and becomes more active during rest. Acute hypoxia may alter the balance between excitatory and inhibitory neurotransmission during cognitive processing. This study investigated GABA+ and Glx changes in the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) during working memory and resting state under normoxia and hypoxia.

Thirty-nine healthy young adults completed two experimental sessions under normoxia (21% O_2) and hypoxia (12% O_2) on separate days. Each session consisted of four alternating 2-back task and resting-state blocks, with two acquisitions from the ACC and two from the PCC.

Compared with normoxia, hypoxia increased Glx levels in both the ACC and PCC across both task conditions. Under hypoxia, GABA+ levels were significantly higher during the 2-back task than during rest in both regions. Under normoxia, ACC Glx levels were significantly lower during the 2-back task than during rest, whereas this task-dependent modulation was not observed under hypoxia.

These findings suggest that acute hypoxia enhances excitatory neurochemistry in the ACC and PCC while altering task-dependent excitatory and inhibitory neurochemical responses. The results provide new insights into the neurochemical mechanisms underlying transitions between cognitive engagement and rest.

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

Project No.: NHRI-EX115-11323EI

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 a progressive degenerative joint disease that is commonly treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or intraarticular hyaluronic acid injections. However, these treatments mainly provide symptomatic relief and have limited ability to prevent cartilage degeneration or modify disease progression. Platelet lysate (PL), which contains abundant growth factors, cytokines, and trophic factors, has attracted increasing attention as a regenerative therapeutic candidate for cartilage repair. Despite its therapeutic potential, direct intraarticular administration of PL is limited by rapid diffusion from the joint cavity, poor protein stability, short bioactive duration, and the potential risks associated with repeated injections.To overcome these limitations, this study developed a micro/nano-scale PL delivery platform stabilized through cold atmospheric plasma (CAP)-induced crosslinking of F127, glycol chitosan, and hyaluronic acid. Unlike conventional approaches that simply incorporate PL into scaffold matrices, this strategy rationally integrates the intrinsic biological activity of PL with a CAP-enhanced biomaterial design. The engineered formulation is expected to improve structural stability, prolong PL retention, enable sustained bioactive factor release, and enhance delivery efficiency within diseased joint tissues.The physicochemical characteristics, release behavior, biological functions, and therapeutic mechanisms of this PL-based delivery system were systematically evaluated using both *in vitro* and *in vivo* OA models. Overall, this work presents a novel CAP-stabilized PL delivery strategy that may maximize the regenerative potential of PL and provide a promising biomaterial-based approach for osteoarthritis treatment.

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

Project No.: NHRI-EX115-11324EI

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, 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

Affiliation/Institution: National Yang Ming Chiao Tung University

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

Building on Aim1, we extended our deep-learning TAVI-planning framework from single-phase landmark detection to a fully automated, full-cardiac-cycle pipeline that localizes aortic-valve hinge points, coronary ostia, and the annulus plane across ten temporal phases. For Aim2, in a 147-patient TAVR cohort, spatial CT features describing calcium distribution relative to the annulus, LVOT, and planned valve frame improved discrimination for conduction disturbance and new LBBB beyond clinical variables alone, a signal confirmed with a tabular foundation model. For Aim3, we integrated endpoint-specific predictive signatures of post-TAVR conduction outcomes from a 231-patient registry with an availability-aware adaptive ensemble for coronary CT angiography triage, extending our framework toward postoperative adverse-event risk stratification. **Introduction:** Aortic stenosis is a common, potentially fatal valvular disease whose prevalence rises with age, and TAVI has become the preferred treatment given its minimally invasive nature. Single-phase cCTA measurements overlook dynamic annulus and calcific deformation across the cardiac cycle, increasing mis-sizing risk and complications such as paravalvular leak and conduction disturbance, and global calcium volume alone poorly predicts these complications. A fully automated framework is therefore needed—one that localizes anatomy throughout the cycle, represents calcification as a local, device-referenced phenotype, and integrates these phenotypes with clinical, procedural, and device data to stratify postoperative adverse-event risk. **Methodology:** For Aim1, we trained a two-step nested U-Net to detect three hinge points and two coronary ostia, and a UNet++ module to segment the annulus plane, across ten cardiac phases in 185 TAVI cases, comparing 2-, 5-, and 10-phase training compositions against manufacturer-guideline sizing. For Aim2, in 147 TAVR cases we expressed calcium components and annular/LVOT geometry in a local coordinate frame across ten phases, compared clinical-only versus clinical-plus-spatial-CT models via repeated cross-validation, and re-evaluated the same spatial core with a tabular foundation model. For Aim3, in a 231-patient TAVR registry we modeled three conduction endpoints using clinical, procedural, and device predictors with cross-validated SHAP, then extended this logic into an adaptive ensemble triaging 864 patients for coronary CT angiography from clinical and low-dose CT features. **Results:** For Aim1, the 10-phase model achieved low localization errors (1.92 mm at hinge points, 1.30 mm at coronary ostia), an annulus area MAE of 13.06-14.27 mm^2, and 84.8% sizing agreement with manufacturer guidelines; full-cycle tracking showed maximal annular dimensions occurring over 10-40% R-R rather than the conventional mid-systolic peak. For Aim2, spatial CT calcium/geometry features raised discrimination for conduction disturbance (AUROC 0.620→0.682) and new LBBB (0.673→0.689), but not paravalvular leak (0.521→0.546); a tabular-foundation-model re-analysis further improved discrimination for both conduction endpoints (0.714 and 0.733). For Aim3, procedural/device variables improved the early conduction composite (0.56→0.78) and new LBBB (0.63→0.82) but not cumulative incident PPM (0.79→0.79), which instead was driven by baseline/rhythm features, and our adaptive ensemble outperformed a hard-availability router for CCTA-yield triage (AUROC 0.807 vs. 0.788; Brier 0.141 vs. 0.153).

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

Project No.: NHRI-EX115-11325EI
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)

Abdominal aortic aneurysm (AAA) is commonly treated using stent grafts that restore blood flow and isolate the weakened vascular wall from systemic pressure, thereby reducing the risk of rupture. However, insufficient mechanical properties may lead to implant migration and subsequent endoleak, which remain important clinical challenges. Therefore, improving the radial compliance and longitudinal flexibility of stent grafts is essential for enhancing treatment outcomes. In this study, an innovative high-entropy alloy (HEA)-based stent graft was developed for AAA repair, consisting of a metallic scaffold and a polymeric membrane.

A NiTiZrHfCu HEA was fabricated through powder metallurgy, vacuum melting, heat treatment, and quenching processes. Different quenching conditions were applied to investigate their effects on material properties. Surface morphology, elemental distribution, crystal structure, mechanical properties, corrosion resistance, and cytocompatibility were systematically evaluated. In addition, polyvinyl butyral (PVB) electrospinning membranes were characterized by tensile testing and permeability assessment. Several zigzag stent geometries were further designed and evaluated using finite element analysis and experimental radial compression testing.

The results showed that heat treatment reduced surface defects and improved elemental homogeneity of the HEA. X-ray diffraction analysis revealed the presence of Ti_2Ni-like, B2 austenite, and B19' martensite phases, while repeated quenching promoted elemental redistribution and phase homogenization. Mechanical testing demonstrated that the Q1 group exhibited the highest elastic recovery rate of 41.3% and showed improved resistance to both elastic and plastic deformation based on H/E and H^3/E^2 analyses. Electrochemical measurements indicated that all groups possessed favorable corrosion resistance, with corrosion current densities remaining on the order of 10^{-6} A/cm².

Cell studies demonstrated that all material groups exhibited satisfactory cytocompatibility, with cell viability exceeding 85% after one day of culture and exceeding 100% after three days in all heat-treated groups. Surface adhesion observations further confirm successful attachment and spreading of vascular smooth muscle cells on all material surfaces. Moreover, heat-treated groups showed reduced smooth muscle cell migration compared with the control group. For the PVB membrane, wet conditions resulted in increased elongation and reduced Young's modulus compared with dry conditions, indicating improved flexibility in hydrated environments. The membrane also exhibited moderate moisture permeability and maintained water resistance below 8.8 mmHg. Finally, finite element simulations and experimental compression tests showed consistent trends among all stent designs, and the S3 configuration demonstrated superior compressive performance due to its more uniform stress distribution.

In conclusion, the combination of the HEA scaffold and PVB membrane demonstrated favorable mechanical properties, corrosion resistance, cytocompatibility, membrane compliance, and structural performance. These findings provide important references for the development of stent grafts for AAA repair and contribute to future preclinical investigations of HEA-based cardiovascular implants.

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

Project No.: NHRI-EX115-11326EI

P.I.: Wen-Chuan Kuo/郭文娟

Affiliation/Institution: National Yang Ming Chiao Tung University

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

Oral cancer has remained among the top ten cancers in Taiwan since 1991. Current screening depends mainly on visual and tactile examination followed by biopsy, but rapid, objective tools for distinguishing benign from malignant lesions are still limited. Optical coherence tomography (OCT), which enables label-free, large-area, depth-resolved imaging, has strong potential to support early oral cancer diagnosis.

Although conventional OCT provides high-resolution structural information, early malignant transformation in oral mucosa often involves subtle stromal remodeling, epithelial disorganization, and collagen matrix changes that may not be fully captured by intensity-based imaging alone. Polarization-sensitive OCT (PS-OCT) can extend conventional OCT by detecting tissue birefringence, depolarization, and polarization-axis alterations, thereby revealing microstructural and extracellular matrix changes associated with dysplasia and tumor invasion. These advantages motivated the development of a multi-contrast PS-OCT approach for oral cancer detection and margin assessment.

We developed a multi-contrast handheld polarization-sensitive OCT (PS-OCT) system to evaluate cancer-associated stromal changes. The system integrates differential intensity, differential phase retardation, degree of polarization uniformity (DOPU), and fast-axis information, and was assessed in healthy human oral tissue and *ex vivo* oral cancer specimens, including normal tissue, dysplasia, and carcinoma in situ. The resulting functional images were compared with histological sections and demonstrated the ability of multi-contrast PS-OCT to differentiate normal from malignant lesions, supporting its use in future *in vivo* clinical studies.

The three-year project is structured as a stepwise translation pathway. In Year 1, multi-contrast PS-OCT and derived quantitative parameters were validated in an animal model through longitudinal imaging of disease progression. In Year 2, a real-time handheld PS-OCT prototype was developed, tested, and optimized using *ex vivo* human specimens. In Year 3, the handheld probe will be evaluated for *in vivo* oral cavity scanning in human subjects.

In summary, this project advances multi-contrast PS-OCT toward a practical, non-invasive imaging tool for early oral cancer detection and tumor margin assessment. By combining structural, polarization, and quantitative contrasts in a handheld real-time platform, the system may complement conventional examination and biopsy, improving diagnostic confidence and supporting future clinical translation.

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

Project No.: NHRI-EX115-11327EI
P.I.: Yuan Luo/駱遠
Key Professional Personnel: Chen Wen Shiang/陳文翔, Ting Chen Chang/張庭蓁, Yu Hsin Chia/賈予鑫, Cheng Hung Chu/朱正弘, Sunil Vyas
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

Conventional structured illumination-based HiLo endomicroscopy faces significant challenges in achieving both system miniaturization and fast acquisition. This bottleneck arises from bulky optical components, which hinder system miniaturization, as well as from time-intensive axial scanning and dual-frame HiLo acquisition schemes that limit imaging speed. Traditional zoom lenses rely on multiple composite elements, making them challenging to miniaturize, while liquid lenses are prone to gravity-induced instability during vertical imaging. To address these limitations, we present a high-resolution AI assisted varifocal endomicroscopy for *in-vivo* brain imaging using metalens. The system incorporates a pair of cascaded high-efficiency GaN metasurfaces positioned at the Fourier plane to form a telecentric configuration, addressing the challenge of system miniaturization while preserving flexible focusing capability. By applying a relative rotation (θ) between the two metasurfaces, the focal length of the system can be precisely tuned from ~15.5 to ~21.6 mm. To overcome the slow acquisition speed inherent in conventional HiLo microscopy, which typically requires acquiring both a uniform-illumination image (I_{uni}) and a structured-illumination image (I_s) to extract full-band in-focus information, a Residual Network (ResNet) model is employed to enable single-shot HiLo reconstruction. The trained ResNet model is used to directly predict the optically sectioned image (I_{HiLo}) by synthesizing the high-frequency and low-frequency components from a single wide-field input, thereby eliminating the need for dual-frame acquisition or background noise. Figure 2 shows *in-vivo* fluorescence imaging of the mouse brain. Using a trained ResNet model, wide-field inputs are directly transformed into optical sectioning images. Experimental validation on *in-vivo* mouse brain and nerve tissues demonstrates an average peak signal-to-noise ratio (PSNR) of ~25.62 dB and a structural similarity index (SSIM) of ~0.78. Furthermore, the ResNet model reduces acquisition time to approximately 0.1 s while maintaining high image quality. These results represent a significant improvement over wide-field inputs, effectively suppressing defocus noise.

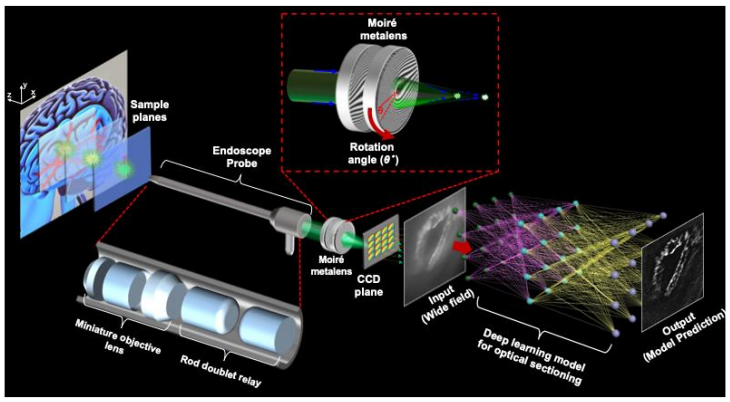

Fig.1 System structure

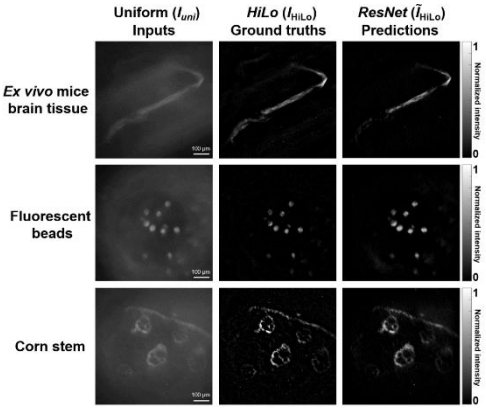

Fig.2 *In-vivo* mouse brain image

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Title of Project: Objective Measurement-based Cochlear Implant Programming
Project No.: NHRI-EX115-11328EI
P.I.: Charles Tak Ming Choi/蔡德明
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, recipients undergo an initial fitting, or mapping, session. During this session, the audiologist determines the most comfortable level (MCL) for each of the 16 electrodes. Conventional fitting relies primarily on behavioral feedback, in which the recipient indicates whether each stimulus is audible and comfortably loud. Although this procedure is time-consuming even for adults, it is particularly challenging for infants and toddlers, who represent approximately 40–50% of new CI recipients annually and often lack the communication skills required to provide reliable responses.

Behavioral fitting remains the clinical gold standard; however, it is labor-intensive. For pediatric CI users, obtaining MCLs for only four electrodes—typically sampled from the apical, mid-apical, mid-basal, and basal regions—requires approximately two hours. In older children and adults, the same procedure typically requires 60–90 minutes. The four measured MCLs are then interpolated to estimate values for the remaining 12 electrodes. This interpolation approach results in an average MCL estimation error of approximately 7–8%, with errors reaching as high as 35% in some cases.

This clinical burden is further compounded by postoperative changes in MCLs. During the first year after implantation, MCLs often drift and require repeated readjustment, typically five to six times, before stabilizing approximately 8–12 months after surgery.

These limitations highlight an unmet clinical need for a non-behavioral fitting approach that reduces stress for young CI users, particularly those aged 1–6 years, as well as an autonomous fitting system that reduces clinic time for CI users across age groups.

To address this need, we propose a patient-specific cochlear implant model, or 個人化人工耳蝸模型. This approach combines limited behavioral data with objective measurements. Behavioral MCLs are measured at four evenly spaced electrodes, while objective measurements are acquired from the remaining 12 electrodes. A patient-specific computational model is then used to predict MCLs for the 12 electrodes without behavioral measurements.

In the third year of the project, we completed patient-specific cochlear implant models for 30 Advanced Bionics CI users, incorporating 18 million numerical cell models. These results represent a substantial advancement over the 6 million-cell model framework reported in the second year. The improved modeling results will be presented in the poster.

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

Project No.: NHRI-EX115-11329EI
P.I.: Yu-Chen Hu/胡育誠
Key Professional Personnel: Yu-Chen Hu/胡育誠
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2024 to 2026 (Total: 3 years)

PEG10 protein was recently uncovered to self-assemble and self-package its own mRNA into nanoparticles, but the particles require expensive transfection for production and have yet to be explored for cancer therapy. Here we develop a human PEG10-based nanoparticles (PBNPs) platform for cargo RNA self-packaging and delivery for cancer therapy. We design a process to improve the PBNPs production for 11.3-fold while reducing the cost. The PBNPs self-package mRNA of at least 7336 nucleotides and remain stable for 7 months. We engineer the PBNPs surface and significantly improve mRNA delivery efficiencies to various cancer cells, particularly colon cancer cells (≈71%). We further reprogram the PBNPs to deliver an immunotherapeutic mRNA cocktail to colon cancer cells, which elicits T cell responses *in vitro*. *In vivo* co-administration of the engineered PBNPs and chemo-drug in female mice synergizes immune responses and promotes anti-cancer efficacy, implicating the potential of PBNPs as an RNA delivery vehicle for immunotherapy.

Keywords: PEG10, protein-based nanoparticles, mRNA delivery, cancer therapy, immunotherapy

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-EX115-11404EI
P.I.: Yao-An Shen/沈耀安
Key Professional Personnel: Yu Hsin Lin/林妤芯, Zhu-Chen Hung/洪子宸, Leu-Wei Lo/羅履維
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Pancreatic ductal adenocarcinoma (PDAC) lethality is driven by therapy-induced adaptive states that fuel chemoresistance and metastasis. Here, we demonstrate that the frontline chemotherapeutic gemcitabine paradoxically upregulates the transcription factor PBX1, triggering a self-sustaining PBX1-NANOG-ZEB1 positive feedback loop that expands the cancer stem cell (CSC) population. We hypothesize that this circuit operates as a closed-circuit Metabolic-Epigenetic Self-Reinforcing Loop (MESL): ZEB1 orchestrates glycolytic reprogramming by activating HK2, PFKP, and PKM2 while suppressing SIRT3; the resulting histone and non-histone lactylation in turn amplifies PBX1, NANOG, and ZEB1 transcription. Simultaneously, this MESL dictates an immune-evasive program: ZEB1 de-represses PD-L1 and CD47 via miR-200 suppression, while lactylation stabilizes PD-L1 through the POM121/MYC axis, shielding CSCs from immune surveillance.

To exploit this metabolic vulnerability, we engineered pH-responsive mesoporous silica nanoparticles (MSN–PBX1i) encapsulating dual small-molecule PBX1 inhibitors. MSN–PBX1i bypasses conventional hENT1-dependent uptake deficits by exploiting transporter-independent, KRAS-driven macropinocytosis. Targeted PBX1 inhibition systematically collapses the MESL, concurrently restoring hENT1-mediated gemcitabine sensitivity and dismantling the immune-evasive shield. Consequently, MSN–PBX1i acts as a state-selective nanotherapeutic that converts a major resistance mechanism into an actionable vulnerability, triggering a tripartite cascade of tumor dismantlement, stromal remodeling, and robust immune reactivation. By uncovering the molecular architecture of therapy-induced plasticity, this work establishes a translatable strategy to overcome therapeutic resistance and subvert immune evasion in PDAC.

Title of Project: Advancing Boron Neutron Capture Therapy for Pancreatic Cancer: Development of Stimuli-responsive and Multifunctional Boron Nanodrugs

Project No.: NHRI-EX115-11417EI
P.I.: Pei Yuin Keng/龔佩雲
Key Professional Personnel: Wei-Ting Yi/易韋廷, Wen-Che Tsai/蔡文哲
Affiliation/Institution: National Tsing Hua University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Development of Stimuli-Responsive Boron Nanomaterials for Targeted Boron Neutron Capture Therapy (BNCT)

Pancreatic ductal adenocarcinoma (PDAC) and triple-negative breast cancer (TNBC) remain among the most difficult malignancies to treat owing to dense stromal barriers, poor drug penetration, and highly immunosuppressive tumor microenvironments. To address these challenges, our research develops stimuli-responsive boron nanomedicines that combine the exceptionally high boron payload of boron carbon oxynitride (BCNO) nanoparticles with transformable nanotechnology to enhance boron neutron capture therapy (BNCT) and stimulate systemic antitumor immunity.

Our laboratory has developed a transformable boron nanoplatform through the self-assembly of BCNO nanoparticles with an acid-responsive polymer. The optimized nanoassemblies remain stable during systemic circulation (~94 nm) but undergo pH-triggered disassembly into ~20 nm nanoparticles within the acidic tumor microenvironment, promoting enhanced tumor penetration and intracellular boron delivery. Owing to the high boron content of BCNO (~38 wt%), the nanoassemblies achieved 21.3-fold higher intracellular boron uptake than the clinical boron agent boronophenylalanine (BPA) and 18-fold greater tumor boron accumulation in orthotopic TNBC models despite using natural-abundance boron. This enhanced delivery translated into an approximately 11-day tumor growth delay, compared with 2.5 days for BPA. Furthermore, BNCT induced immunogenic cell death and, when combined with anti-PD-L1 immune checkpoint blockade, suppressed spontaneous pulmonary metastasis by more than 93%, demonstrating the synergistic potential of integrating high-boron nanomedicine with immunotherapy to convert localized neutron irradiation into systemic control of metastatic disease.

Building upon these achievements, we are extending this platform toward PDAC by developing folic acid-targeted, stimuli-responsive BCNO nanoassemblies. We have established PANC-1 cell culture, an orthotopic pancreatic cancer mouse model, ultrasound-guided tumor monitoring, and initiated pilot biodistribution studies. Leveraging our tunable self-assembly methodology, which enables precise control of nanoparticle size and surface charge, we will systematically identify the optimal physicochemical properties for maximizing boron delivery and BNCT efficacy against PDAC. This work establishes a versatile BNCT nanomedicine platform that integrates high boron loading, tunable nanoparticle engineering, and immunotherapy to overcome stromal transport barriers in refractory solid tumors while providing design principles for next-generation precision BNCT against TNBC and PDAC.

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

Project No.: NHRI-EX115-11418EC

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)

Closed-loop transcranial magnetic stimulation (CL-TMS) aims to improve neuromodulation by timing stimulation according to ongoing brain activity. Intermittent theta burst stimulation (iTBS) is a time-efficient protocol for treatment-resistant depression, but conventional iTBS is usually delivered in an open-loop manner, with burst trains applied at fixed intervals independent of instantaneous neural state. Phase-triggered CL-TMS may improve individualization by aligning stimulation with endogenous EEG rhythms. However, closed-loop iTBS (CL-iTBS) requires accurate causal theta-phase estimation, stable burst timing, and validation methods that remain reliable despite TMS-induced EEG artifacts.

This work presents the design and validation of a phase-triggered CL-iTBS system integrating EEG acquisition, online processing, and TMS triggering. EEG was recorded using a 32-channel cap and actiCHamp amplifier, streamed through LabStreamingLayer, processed in MATLAB, and used to control a Magstim Rapid2 stimulator. The pipeline extracted a two-second EEG window and estimated theta phase from a prefrontal F3-Fz signal. The first iTBS triplet was aligned to a target theta phase, allowing the burst train to coordinate with ongoing oscillatory activity.

We evaluated six causal phase-estimation algorithms, including Fourier-based forecasting, autoregressive prediction, Educated Temporal Prediction, Endpoint-Corrected Hilbert Transform, and forecast-padding variants. To reduce deadlocking, we introduced a combined triggering strategy. The system normally used range triggering, delivering stimulation when the estimated phase fell within a tolerance window around the target. If no valid trigger occurred after a predefined threshold, it switched to timer triggering, estimating delay from the phase difference and individual theta frequency.

Validation included offline in-silico simulation and online in-vitro phantom testing. Simulations used prerecorded resting-state EEG and evaluated four target phases: 0°, 90°, 180°, and 270°. ARFP achieved the lowest phase-estimation error, followed by ECHT. ARFP performed especially well for 90° and 270°, while ECHT performed best for 0° and 180°. Inter-trigger intervals remained stable, indicating no severe deadlocking. In the saline phantom experiment, prerecorded EEG was replayed, re-recorded, and used to trigger real TMS pulses. Online results closely matched offline simulations using the same phantom signals, supporting delay compensation and validation. Overall, this study demonstrates that phase-triggered CL-iTBS can achieve accurate and stable stimulation timing through joint design of phase estimation, triggering logic, and system validation.

Title of Project: Personalized Network-based Machine Learning Model Builds Digital Twins for Predicting Anti-cancer Drug Efficacy in Head and Neck Cancer Patients

Project No.: NHRI-EX115-11429EI

P.I.: Chun-Yu Lin/林峻宇

Key Professional Personnel: Chun-Yu Lin/林峻宇, Jih-Chin Lee/李日清, and Ding-Jie Lee/李定頡

Affiliation/Institution: National Yang Ming Chiao Tung University

Entire Project Period: From 2025 to 2027 (Total: 3 years)

Head and neck squamous cell carcinoma (HNSCC) shows substantial inter-patient heterogeneity, making it difficult to predict individual responses to anti-cancer therapies using conventional biomarkers. Supported by this project, we developed INSPIRE, an interpretable patient-specific network-based machine-learning framework for therapeutic response prediction from pre-treatment transcriptomic profiles. INSPIRE first applies the sample-specific weighted correlation network (SWEET) framework to infer single-sample networks (SINs) for individual patients. For each drug of interest, INSPIRE intersects SINs with a high-confidence protein–protein interaction network and applies network propagation from its targets to identify patient-specific drug-affected subnetworks. ssGscore further quantifies the association strength between these subnetworks and biological pathways to define personalized drug-response pathway signatures, while ssGSEA estimates pathway activity in each patient. These complementary pathway-level features are then integrated for machine-learning model training and response prediction.

Because public immunotherapy datasets with sufficient clinical response annotations are more readily available in melanoma, we first evaluated INSPIRE across multiple independent immune checkpoint inhibitor-treated melanoma cohorts. INSPIRE showed robust cross-cohort performance, outperforming conventional tumor microenvironment signatures and aggregate network-based baselines, with a best AUC of 0.82. SHAP analysis further identified recurrent immune-related inflammatory pathways contributing to individual predictions. To better align with the original goal of predicting anti-cancer drug efficacy in HNSCC, we further applied INSPIRE to cisplatin-treated HNSCC patients. Using TCGA HNSCC samples for training and an independent HNSCC cohort from Tri-Service General Hospital for testing, INSPIRE achieved an AUC of 0.75, outperforming NetBio and a conventional cisplatin-response baseline.

In summary, INSPIRE provides an interpretable patient-specific network-based machine-learning framework that can be generalized from immunotherapy response prediction to chemotherapy response prediction in HNSCC, supporting the development of personalized drug-efficacy prediction strategies for precision oncology.

Title of Project: Ultrasound Super Resolution Microvascular Imaging for Evaluating the Treatment Performance of Transcatheter Arterial Microembolization in Chronic Musculoskeletal (MSK) Pain of Finger and Wrist.

Project No.: NHRI-EX115-11430EI
P.I.: Chih-Chung Huang/黃執中
Key Professional Personnel: Fong-Chin Su/蘇芳慶, Chein-Kuo Wang/王建國, Tai-Hua Yang/楊岱樺, Bow Wang/王博
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Chronic musculoskeletal pain is a common and difficult-to-treat condition for clinicians and patients and is caused by a variety of conditions affecting bones, muscles, ligaments, tendons, and joints. It is estimated that 20-33% of people worldwide suffer from chronic musculoskeletal pain, which often results in reduced activity, sleep disturbance, fatigue, mood changes, and severe disability. Recently, trans-arterial micro-embolization (TAME) has been proposed as a minimally invasive procedure used to block the target blood vessels by injecting an embolic agent, which can cure various chronic painful musculoskeletal conditions that are refractory to conservative treatment. Therefore, this proposal proposes the first time of using ultrasound as an imaging modality for monitoring TAME surgery due to its advantages of real time, non-invasiveness, and no radiation exposure, it is very suitable for monitoring the neovascularization during the TAME surgery or for the follow up monitoring. However, even if high-frequency ultrasound (>30 MHz, HFUS) is used for neovascularization imaging, the image resolution for microvasculature visualization is still insufficient. Therefore, the main purposes of this project are to develop a super-resolution ultrasonic blood flow imaging that is so-called contrast-free erythrocytes ultrasound localization microscope (eULM) based on HFUS for replacement of X-ray angiography in TAME surgery. The technique integrates high-frequency (40 MHz) ultrasound with flow-aware erythrocyte tracking and Hessian-based vesselness filtering. It was first validated in a rat kidney model using varying doses of imipenem/cilastatin (IPM-CS) for TAME. Subsequently, three patients with refractory de Quervain's tenosynovitis were imaged before TAME and at 14 days and 3 months post-treatment. Imaging biomarkers, including vessel density (VD) and flow velocity, were correlated with clinical pain (NRS) and function (PRWE) scores. In animal study, the imaging method achieved a resolution of 6.41 μm and an SNR of 82.73 dB, capturing dose-dependent embolization. In clinical subjects, FA-Hessian eULM visualized dense neovascular networks before treatment that were significantly reduced following TAME. A strong correlation was found between VD and PRWE scores (r_{within} = 0.99, $p < 0.001$), confirming the clinical relevance of the imaging metrics. FA-Hessian eULM provides high-resolution, quantitative visualization of microvascular dynamics without contrast agents. It may serve as a promising objective tool for assessing treatment efficacy and longitudinal response to TAME in de Quervain's tenosynovitis.

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: A Fully Automated MALDI-TOF-Based Antimicrobial Resistance Prediction System

P.I.: Hsiao-Hui Tsou/鄒小蕙
Presenter: Yi-Kai Chen/陳怡凱, Cheng-Hsiung Chiang/姜正雄
Institute/Center: National Health Research Institutes

Antimicrobial resistance (AMR) is a major global health challenge. Although MALDI-TOF mass spectrometry has shown potential for AMR prediction, conventional data processing workflows often depend on proprietary software and manual operations. To overcome these limitations, we developed a fully automated MALDI-TOF-based antimicrobial resistance prediction system that transforms raw binary data into spectra, performs peak detection and mass-list generation, and directly outputs antimicrobial resistance classification results without requiring commercial software, such as flexAnalysis. The proposed automated system process includes six steps: (1) converting binary raw data into spectra; (2) detecting peaks in the spectra using the developed peak detection method; (3) calculating data such as intensity, area, and signal-to-noise ratio (SNR) to establish a mass list; (4) establishing training samples for the machine learning model using the applied feature alignment algorithm; (5) training the machine learning model; and (6) classifying whether the obtained mass spectrometry data has antimicrobial resistance. We applied the three feature alignment methods: a fixed binning method, a custom binning method, and an HDBSCAN clustering method. The resistance classification performance of these three methods can be used to evaluate and determine which method to use. The development of the automated system at each stage (there are a total of six stages) has been successfully completed, and each stage can stably generate the expected data. The main contributions of this study are: (1) improving analysis efficiency and saving time (flexAnalysis requires manual operation, while the developed program is fully automated); (2) flexible feature settings (the interval width and feature filtering conditions can be adjusted), which in turn affects the number of features and model performance; (3) developing the program independently, without being limited by flexAnalysis, and moving towards full automation of the process. In the future, we will integrate the six-stage process of the automated system, hoping to develop a one-click solution that allows the automated system to automatically complete the six-step process when conditions are triggered.

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

Project No.: NHRI-EX115-11202PI
P.I.: Ming-Tsang Wu/吳明蒼
NHRI Researcher: Chu-Chin 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 (CKD) is a major public health burden, and Taiwan has the highest global incidence of treated end-stage renal disease (ESRD). Emerging evidence suggests that environmental exposure to melamine and its analogue, cyanuric acid (CYU), may adversely affect renal health in children, yet data on this association in school-aged populations remain limited.

Method: Using data from the Taiwan Maternal and Infant Cohort Study (TMICS), an ongoing multicenter birth cohort initiated in 2012, we analyzed 569 children aged 8-12 years (318 boys, 251 girls) with complete urinary data on melamine, CYU, and renal injury biomarkers. Renal impairment was assessed using the albumin-to-creatinine ratio (ACR), N-acetyl-β-D-glucosaminidase (NAG), and β2-microglobulin (B2M). Logistic regression models, stratified by exposure cutoffs (75th vs. 25th percentile, and 90th vs. 10th percentile) and by sex, were used to estimate associations between melamine/CYU exposure and renal biomarkers.

Results: Among the 569 children (mean creatinine-adjusted melamine: 1.56 ± 2.93 μg/mmol cr; CYU: 14.79 ± 41.69 μg/mmol cr), boys and girls differed significantly in creatinine, ACR, NAG, and B2M levels (all $p<0.05$). Using logistic regression models with melamine daily intake (Melamine_DI) and CYU as binary exposure indicators (high vs. low, at both 75%/25% and 90%/10% cutoffs) and logACR, logNAG, and logB2M as outcome variables, higher exposure to both chemicals was associated with increased renal injury markers. CYU showed the most consistent and significant associations across all three biomarkers and both cutoff definitions, while melamine showed significant associations primarily with logACR and logNAG. Sex-specific renal risks were observed for melamine exposure, but not for CYU exposure.

Conclusion: Both melamine and CYU were associated with elevated renal injury biomarkers among school-aged children, with CYU exhibiting stronger effects than melamine. An early, sex-specific renal risks related to melamine, but not CYU, exposure were observed in children and warrant further investigation.

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

Project No.: NHRI-EX115-11208PI

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 that promote a sustainable kidney health system.

Materials and Methods: Building on this model, we integrated cost data and clinic-derived utility estimates to conduct a cost-effectiveness analysis from the government payer perspective. Four predefined CKD care referral policies were compared: Policy A, referral of all screen-detected CKD patients aged ≥65 years to CKD care programs; Policy B, referral of all screen-detected CKD patients with CKD stage 3b or higher; Policy C, referral of patients meeting both Policy A and Policy B criteria; and Policy D, referral of patients meeting either Policy A or Policy B criteria. Lifetime CKD care program costs and quality-adjusted life years were compared with those under the screening-only program. In addition, risk equations and calculators were developed to estimate transitions across CKD stages, end-stage kidney disease, and death.

Results: Among the four policies, Policy A was the most broadly cost-effective strategy, with an incremental cost of NT$1,197 per quality-adjusted life-year gained. Policy C was associated with a higher incremental cost-effectiveness ratio (ICER) of NT$2,276. In analyses stratified by baseline risk of adverse outcomes, Policy A showed relatively consistent ICER values across risk groups, whereas Policies B and D became more cost-effective among patients at the highest risk of adverse outcomes. The cost-effectiveness acceptability curve showed that all policies reached more than 80% probability of cost-effectiveness at a willingness-to-pay threshold below NT$5,000, while Policy A approached 100% probability at a threshold below NT$15,000. In addition, CKD risk calculators were developed for different initial CKD stages to estimate transition probabilities across CKD stages, end-stage kidney disease, and death.

Conclusion: The framework integrates CKD disease-transition risk equations, cost data, and utility estimates to inform sustainable kidney health policy. Among the predefined referral strategies, referral of all screen-detected CKD patients aged ≥65 years to CKD care programs appeared to be the most broadly cost-effective policy, with a low ICER and high population coverage. The accompanying CKD risk calculators may help governments, clinicians, patients, and caregivers estimate transition probabilities across CKD stages, ESKD, and death, thereby supporting precision referral strategies and efficient allocation of CKD care resources.

Keywords: chronic kidney disease, cost-effectiveness analyses, risk equations, care resources.

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

Project No.: NHRI-EX115-11209PI

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 in service provision.

Purpose: The 3rd and 4th years of this project are aimed to design a needs-based competence training program for older volunteers providing community-based long-term care services and to evaluate its effectiveness in improving volunteer-related knowledge and skills, motivation, self-efficacy, and work satisfaction.

Methods: In the 3rd year, the Delphi method was employed to develop and refine the training program through iterative evaluations conducted by 10 experts until consensus on content validity was achieved. In the 4th year, a cluster-randomized controlled trial is being conducted. Ten senior activity centers and 162 older volunteers have been recruited and randomized into either the intervention group (IG) or the wait-list comparison group (CG). Currently, participants in the IG are receiving 3-hour weekly training sessions over four consecutive weeks. Following the training, the older volunteers will provide services to community-dwelling older adults for two months, while the CG continues routine services at the senior activity centers.

Results: The Delphi panel consisted of 2 center directors, 2 older volunteers, and 2 experts each in geriatric nursing, social work, and education. The 10 experts had a mean age of 59.40 years (*SD* = 9.20) and 90% were female. Most held doctoral degrees (60%) and had an average of 19.39 years (*SD* = 9.94) of professional experience working with older volunteers. Two rounds of Delphi consultations were conducted. In the first round, the item-level content validity index (I-CVI) exceeded 0.80, while the scale-level content validity index using the averaging calculation method (S-CVI/Ave) exceeded 0.90 for both content feasibility and appropriateness. Based on expert feedback, the program was revised in five areas: (1) comprehensibility of course content; (2) specificity; (3) applicability; (4) diversity of teaching methods; and (5) practicality of task implementation. In the second round, all I-CVI and S-CVI/Ave values reached 1.00 for both content feasibility and appropriateness, indicating full consensus among the experts. The finalized program consisted of four courses: (1) Introduction to Volunteer Service, (2) Promoting Physical and Mental Health, (3) Excelling in Interpersonal Interaction, and (4) Mastering Service Skills. In the 4th year, 162 participants are enrolled (IG: *n* = 85, CG: *n* = 77). Participants have a mean age of 71.20 ± 5.13 years and are predominantly female (84.6%). Most participants (80.3%) have more than five years of volunteer experience.

Conclusion: The comprehensive training program for older volunteers demonstrated excellent content validity based on expert consensus. It is currently undergoing effectiveness evaluation, with participants completing a four-week training program. The findings suggest that this program has strong potential as a practical and effective training model for older volunteers.

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

Project No.: NHRI-EX115-11210PC
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: Stroke is a leading cause of disability worldwide, and approximately 80% of individuals with stroke experience upper extremity (UE) dysfunction. Although home-based rehabilitation programs improve UE function and daily activity performance, translating these evidence-based interventions into routine clinical practice remains challenging. To address this, the Graded Repetitive Arm Supplementary Program (GRASP), an evidence-based home exercise protocol, was utilized.

Purpose: This four-year project aims to: (1) evaluate the implementation of the home-based GRASP program in clinical rehabilitation settings and identify facilitators and barriers, while establishing responsive remote assessment protocols; and (2) compare the effectiveness of therapist-delivered home-based GRASP with standard UE rehabilitation through a multi-center randomized controlled trial (RCT).

Results: During Years 3 and 4, substantial progress was made toward the large-scale implementation of home-based stroke rehabilitation.

First, we evaluated the responsiveness, minimal clinically important difference (MCID), and predictive validity of the Arm Capacity and Movement Test (ArmCAM), a videoconference-based assessment of UE function. ArmCAM demonstrated high responsiveness to change (standardized response mean = 0.92), with MCID estimates ranging from 2.5 to 3.3 points. Baseline ArmCAM scores also showed moderate predictive validity for post-intervention functional outcomes, supporting its use in home-based rehabilitation and telerehabilitation.

Second, we explored the experiences of 18 individuals with stroke participating in the home-based program. Key facilitators included high motivation, perceived accessibility, and the use of wearable feedback, which encouraged greater real-world hand use. Conversely, technological and equipment setup difficulties were identified as primary barriers.

Third, the multi-center RCT comparing front-line occupational therapist-delivered home-based GRASP with standard rehabilitation has enrolled 59 participants across three hospital sites. Participants in the intervention group perform one hour of daily GRASP exercises over four weeks with therapist supervision three times weekly. To date, 45 participants have completed the study, 11 are undergoing intervention or follow-up, and 3 have withdrawn.

Conclusions: The project has successfully established a responsive remote assessment tool for home-based rehabilitation, identified factors influencing participant engagement, and implemented a multi-center RCT across three rehabilitation sites. These findings support the feasibility of scaling out the GRASP program in real-world clinical settings. Completion of the ongoing trial will provide evidence regarding the effectiveness of front-line occupational therapist-delivered home-based GRASP and inform future implementation strategies for stroke rehabilitation.

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

Project No.: NHRI-EX115-11304PI

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 2011 to 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. WGS has been done by using the Illumina NovaSeq-6000 platform at the Precision Medicine Research Center, Taipei Medical University.

To date, 2,705 tuberculosis isolates have been successfully sub-cultured for DNA extraction, in which 2,546 isolates have completed WGS, generated 150 bp paired-end reads with a mean mapping rate of 98.68%. Drug resistance and lineage were predicted for 2,542 isolates using TB-Profiler, in which 239 (9.4%) have isoniazid resistance-conferring mutations, in which 133 carried mutations in inhA, 134 in katG, and 5 in the oxyR'-ahpC intergenic region. 92 (3.6%) isolates had mutations in rpoB and 1 in rpoC (rifampicin resistance), 59 (2.3%) isolates had mutations in pncA (pyrazinamide resistance), and 58 (2.3%) isolates had mutations in embB and 2 in embA (ethambutol resistance). For lineage distribution, lineage 4 was the most prevalent (n=1,176, 46%), followed by lineage 2 (n=1,002, 39%) and lineage 1 (330, 13%).

The WGS data completion rate exceeded 90% for most years between 2014 and 2025. Therefore, preliminary analysis of transmission of tuberculosis was performed for 2402 isolates collected during this period using a ≤12 SNP threshold to define genomic clusters. Of the 2,402 isolates, 1,073 (45%) belonged to genomic clusters. These clustered isolates were grouped into 244 clusters, with cluster sizes ranging from 2 to 100 isolates. The largest cluster (n = 100) belonged to lineage 4 and consisted predominantly of drug-susceptible TB, with only two isolates resistant to streptomycin. Compared with lineage 1, isolates belonging to lineage 2 (OR: 2.54; 95% CI: 1.90–3.38) and lineage 4 (OR: 2.02; 95% CI: 1.52–2.68) were significantly more likely to be genomically clustered. Drug-resistant TB was less likely to be genomically clustered than drug-susceptible TB (OR: 0.90; 95% CI: 0.73–1.10).

Compared with females, male patients were significantly more likely to belong to genomic clusters (OR: 1.34; 95% CI: 1.11–1.63). Compared with patients aged ≥65 years, those aged <25 years (OR: 5.19; 95% CI: 3.36–8.00), 25–44 years (OR: 4.35; 95% CI: 3.32–5.70), and 45–64 years (OR: 3.29; 95% CI: 2.71–3.99) were also significantly more likely to be genomically clustered.

Overall, this study integrates epidemiological, microbiological, and WGS data to better understand the epidemiology and transmission of TB in eastern Taiwan.

Title of Project: Harnessing Genomic Information in Public Health to Tackle Tuberculosis
Project No.: NHRI-EX115-11305PI
P.I.: Hsien-Ho Lin/林先和
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2028 (Total: 5 years)

Background: Subclinical tuberculosis (TB) has been increasingly recognized as an important source of transmission. However, transmission occurring before symptom onset is challenging to measure and is poorly quantified, limiting understanding of the epidemiological contribution of subclinical disease. We aimed to estimate the proportion of TB transmission events occurring prior to reported symptom onset using population-based whole-genome sequencing (WGS) data.

Methods: We analyzed culture-confirmed TB cases from a population-based cohort in Kaohsiung, Taiwan, between 2019 and 2023. Mycobacterium tuberculosis isolates underwent WGS, and genomic clusters were defined using a 12 single nucleotide polymorphism threshold. Time-calibrated phylogenies were reconstructed using Bayesian evolutionary analysis (BEAST), and transmission trees were inferred with TransPhyloFork, an adapted TransPhylo framework. Transmission timing between inferred infector–infectee pairs was compared with self-reported symptom onset dates. Pre-symptomatic transmission was defined as transmission occurring before the reported symptom onset of the inferred infector. Subgroup differences were assessed using within-iteration posterior contrasts. Sensitivity analyses were conducted among individuals with a posterior probability greater than 0.3 of being an infector. To assess the robustness of findings to prior assumptions on transmission and sampling timing, additional sensitivity analyses were performed under scenarios varying the generation time and sampling time prior.

Findings: Thirty-six clusters comprising five or more cases, including 462 patients, were included in transmission tree analyses. Across posterior transmission trees, a median of 223 putative transmission pairs were inferred per iteration (IQR: 217–229). Among transmission pairs with available infector symptom onset data, a median of 69.4% (IQR 66.7–72.1%) of transmission events occurred prior to reported symptom onset. This proportion remained consistent across all sensitivity scenarios. The estimated proportion of pre-symptomatic transmission was higher among infectors aged <35 years than among older infectors, was higher in rural and suburban areas than in urban areas, and increased with cluster size. The median interval from reported infector symptom onset to inferred transmission was −174 days (IQR: −415 to 53.1 days).

Interpretation: In this population-based genomic study, a substantial proportion of inferred TB transmission events appeared to occur before reported symptom onset. These findings underscore the epidemiological importance of transmission from subclinical cases and highlight the limitations of passive, symptom-based case-finding strategies in controlling TB. Active case detection strategies that identify individuals irrespective of symptoms may be critical for interrupting transmission chains.

Title of Project: Molecular Diagnostics, Prognostics, Pathogenetics, and Therapeutics of SLC26A4 Variants - a Prevalent Cause of Profound Hearing Impairment in Children
Project No.: NHRI-EX115-11311PI
P.I.: Chen-Chi Wu/吳振吉
Key Professional Personnel: Pei-Hsuan Lin/林珮璇, Cheng-Yu Tsai/蔡政育
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2024 to 2027 (Total: 4 years)

Dynamic Longitudinal Audiological Trajectories for Predicting Acute Hearing Loss in *SLC26A4*-Related Deafness: A Prognostic Machine Learning Approach

Background: Pathogenic variants in *SLC26A4* cause progressive and fluctuating hearing loss. Patients frequently experience unpredictable episodes of acute hearing loss (AHL) that lead to irreversible functional deterioration. Predicting these acute episodes remains difficult due to high phenotypic heterogeneity. This study presents a two-stage machine learning framework using longitudinal audiological data to predict individual AHL risk within a six-month window.

Methods: This prognostic cohort study evaluated 231 patients with enlarged vestibular aqueduct (EVA) and/or pathogenic *SLC26A4* variants followed between 1983 and 2024. Patients with fewer than four audiological records were excluded to ensure sufficient data for trend modeling. The final dataset included 126 patients contributing 3,267 frequency-specific hearing thresholds. Because *SLC26A4*-related hearing loss is frequently asymmetrical, left and right ears were analyzed independently. The predictive architecture consisted of two steps: (1) unsupervised feature engineering using autoencoders and K-means clustering to extract latent time-series morphological "shape" features, combined with prognostic regression features generated via ElasticNet; and (2) binary classification using a Categorical Boosting (CatBoost) fusion engine to predict AHL events.

Results: A total of 381 AHL episodes were recorded (195 in left ears; 186 in right ears). Simultaneous bilateral episodes occurred in only 22% of cases, confirming inter-aural progression asymmetry. Conventional static parameters, including gender, specific *SLC26A4* genotypes, vestibular aqueduct size, and the presence of Mondini dysplasia, showed no significant correlation with AHL occurrence. The integrated fusion model (ElasticNet + CatBoost) achieved optimal performance, demonstrating an area under the curve (AUC) of 0.766 ± 0.032 and an accuracy of 0.702 ± 0.067. Ablation analysis confirmed that removing the automatically derived temporal "shape" features significantly decreased model performance.

Conclusions: This framework demonstrates that longitudinal audiological trajectories provide critical dynamic signals that precede acute exacerbations. By establishing an objective early-warning method, this model can guide proactive clinical management, including personalized monitoring intervals, hearing aid or cochlear implant adjustments, and timely preemptive 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-EX115-11312PC

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/莊雅嫚, 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 gut–brain interaction that substantially reduces quality of life, yet few culturally tailored self-management programs exist in Taiwan. This four-year mixed-methods project (2024–2027) aims to develop and test a comprehensive self-management (CSM) intervention for Taiwanese adults with IBS. Building on first-year findings, which established culturally adapted evaluation measures and demonstrated favorable stakeholder acceptance while identifying areas requiring further cultural refinement, the second year focused on finalizing the intervention and preparing for pilot testing.

Purpose: The second-year aims were to (1) culturally adapt and transform the existing CSM curriculum into a digitally delivered format; and (2) finalize the study procedures, assessment protocols, and biological-specimen workflows required for the pilot randomized controlled trial (RCT).

Methods: The intervention was culturally adapted according to the eight dimensions of the Ecological Validity Model and transformed from a paper-based curriculum into an eight-week digital program consisting of videos, online educational materials, weekly exercises, and electronic symptom diaries. Content underwent iterative multidisciplinary review with nursing, nutrition, psychology, and gastroenterology experts, with nutritional components reframed around individualized dietary strategies rather than blanket restriction. Implementation procedures, staff training, and biological sampling protocols were then established.

Results: The team completed an eight-week digital intervention consisting of eight educational videos, accompanying online learning materials, electronic weekly assignments, symptom-monitoring tools, and five guided relaxation videos. All materials passed expert review for cultural appropriateness and usability. Standardized implementation manuals, staff training materials, and quality-control procedures were completed to ensure intervention fidelity during the pilot trial. The Patient Activation Measure-10 (PAM-10) was licensed, translated into Traditional Chinese, and prepared for use in the pilot trial, and procedures for gut-microbiota and fecal-calprotectin sampling were established and pilot-tested. Eighteen eligible participants have been enrolled, and the pilot RCT has entered the recruitment phase.

Conclusion: The second year successfully completed the culturally adapted digital intervention and the operational infrastructure required for pilot testing. These accomplishments establish a strong foundation for implementation and evaluation of the pilot randomized controlled trial during the remaining project period.

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-EX115-11331PI

P.I.: Wen-Ya Ko/可文亞

Key Professional Personnel: Chao-Kuang Lin/林昭光(泰雅族), Valis Tanapima/田知學(布農族), Yuan-Feng Lin/林源峰(排灣族), Jian-Lian Chen/陳淨蓮, Mei-Ling Kang/康梅鈴, Tsung-Jieh Lo/羅琮絜, Wan-Hsin Chen/陳畹欣

Affiliation/Institution: National Yang Ming Chiao Tung University

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

Taiwan Indigenous peoples represent one of the most genetically diverse yet underrepresented populations in genomic research, limiting the equitable implementation of precision medicine. To establish a genomic foundation for Indigenous health research, we integrated genome-wide SNP genotyping (>2,300 individuals), high-coverage whole-genome sequencing (42 individuals representing seven Indigenous populations), local ancestry inference, and genome-wide scans for recent positive selection to characterize genomic diversity, demographic history, and recent adaptation. Population structure analyses revealed pronounced genetic differentiation among Indigenous populations, demonstrating that they cannot be treated as a single homogeneous genetic group in biomedical research. High-coverage whole-genome sequencing generated a high-quality genomic resource, with mapping rates of 95–97%, average sequencing depths of 35–41×, genome callability exceeding 98%, and approximately 4.9 million variants identified per individual. Analysis of these whole-genome data further revealed elevated long-range linkage disequilibrium across all Indigenous populations relative to Han Taiwanese. The Truku and Bunun populations exhibited particularly slow LD decay, consistent with stronger genetic drift and historically smaller effective population sizes. Local ancestry analyses supported a two-pulse admixture history in the Pingpu Siraya population, with the earliest admixture occurring approximately 250 years ago, consistent with historical records of Han migration into Taiwan. Genome-wide iHS analyses identified numerous population-specific signatures of recent positive selection with limited overlap among populations, suggesting distinct adaptive trajectories shaped by local environments and demographic history. Representative candidate genes included *SMYD3* (hypoxia and oxidative stress) in the Atayal, *GYPA*/*GYPB* (erythrocyte biology and malaria resistance) in the Amis, *FGFR2* (developmental signaling) in the Bunun, and the *ADH* gene cluster (alcohol metabolism) in the Paiwan. These findings establish an important genomic resource for Taiwanese Indigenous populations and demonstrate that fine-scale population structure, demographic history, and adaptive evolution should be incorporated into ancestry-aware variant interpretation, disease gene discovery, and future precision medicine initiatives to promote health equity among Indigenous communities in Taiwan.

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-EX115-11332PI
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)

Emergency department (ED) revisits represent an important patient safety concern, particularly when patients return within 72 hours with serious adverse events such as intensive care unit admission, emergency surgery, or in-hospital cardiac arrest. To improve discharge decision-making, these two complementary studies developed and validated data-driven approaches for predicting general and high-risk ED revisits using dynamic clinical information. The first study applied group-based trajectory modeling to identify clinically meaningful vital sign patterns during the index ED visit, demonstrating that temporal trends, especially a “very high but resolving” heart rate trajectory, were associated with increased odds of both overall and high-risk revisits. Older age and chronic major diseases, particularly cancer, were also important predictors, suggesting that dynamic physiological changes provide additional risk information beyond single-point measurements.

Building on this concept, the second study developed a hybrid deep learning model integrating static clinical variables with short-term dynamic vital sign time-series data. The model combined a temporal convolutional network with an FT-Transformer to address irregular time-series data and better represent changes in patient status during ED care. Using National Taiwan University Hospital ED data from 2016–2019 for model development, the model achieved an AUROC of 0.8453 and AUPRC of 0.0935 for high-risk revisit prediction, and an AUROC of 0.7250 and AUPRC of 0.2005 for general revisit prediction. In the 2020–2022 internal validation cohort, it achieved an AUROC of 0.7976 and AUPRC of 0.0103 for high-risk revisits, and an AUROC of 0.7300 and AUPRC of 0.1537 for general revisits, outperforming a static-only logistic regression baseline. Feature importance analysis further identified heart rate as the most influential predictor.

Together, these studies show that incorporating vital sign trajectories and time-aware deep learning architectures can improve early identification of patients at risk for ED revisits, especially serious high-risk events. These findings support the clinical value of dynamic, longitudinal ED data for enhancing risk stratification, guiding safer discharge decisions, and developing future real-time decision-support tools to reduce preventable adverse outcomes after ED discharge.

The aforementioned deep learning-based model has been uploaded to the emergency department's private cloud (Advantech's Wise-PaaS platform) and enabled for cloud-based inference. Once the IT application is approved, real-time data will be integrated for inference to prospectively validate the model and prepare for the next phase of clinical trials.

Title of Project: Outcomes of Mirror Therapy Preceding Augmented Reality in Stroke Rehabilitation
Project No.: NHRI-EX115-11333PI
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 receiving growing attention in stroke rehabilitation. However, it remains unclear whether MT priming may enhance the effects of AR-based training. This study investigated the effects of AR, with or without MT priming, on sensorimotor function, balance, self-efficacy, and quality of life after stroke.

Methods: A single-blind randomized controlled trial with a 3-month follow-up was conducted across four outpatient rehabilitation clinics. Seventy-seven individuals with first-ever stroke were randomly assigned to receive MT preceding AR (MT+AR; n = 26), AR alone (n = 26), or dose-matched conventional therapy (CT; n = 25). Participants received 90-minute interventions per session, three times weekly for 6 weeks. Primary outcome measures included the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) and Berg Balance Scale (BBS). Secondary outcome measures included measures of sensory function, arm activity and functional use of the affected arm, stroke-specific self-efficacy, and quality of life. Clinical significance of change was evaluated based on the threshold value of minimal clinically important difference (MCID).

Results: The MT+AR group demonstrated greater improvements in motor and sensory outcomes compared with the AR and CT group and showed the highest proportion of participants achieving MCID thresholds. Both MT+AR and AR groups showed greater improvements than CT in balance, functional use of the affected arm, self-efficacy, and quality of life, with significantly more participants reaching clinically meaningful improvements in the FMA-UE and BBS. Improvements were maintained at the 3-month follow-up. No adverse response was reported in this trial.

Conclusions: MT-based priming may enhance the effects of AR in stroke rehabilitation, particularly for motor and sensory recovery. AR-based interventions, with or without MT priming, may provide clinically meaningful benefits for functional recovery and quality of life after stroke. The findings indicated the priming effect of mirror visual feedback on AR interventions. Further research will study the factors predictive of treatment success immediately after MT-primed AR intervention to inform patient selection and precision rehabilitation. Future mechanistic research is needed to study the role of the strength of mirror visual illusion in mediating sensorimotor recovery associated with MT.

Title of Project: Effects of Strategy Training for Physical Activity on Executive Functions in Stroke Survivors with Cognitive Impairments: a Phase II Randomized Controlled Trial
Project No.: NHRI-EX115-11408PI
P.I.: Feng-Hang Chang/張鳳航
Key Professional Personnel: Shih-Pin Hsu/許世賓, Ching-Yi Wu/吳菁宜
Affiliation/Institution: Taipei Medical University
Entire Project Period: From 2025 to 2029 (Total: 5 years)

Poststroke cognitive impairment, particularly executive dysfunction, is a disabling consequence of stroke that significantly impacts individuals' life roles and well-being. Although the literature increasingly supports physical activity interventions, their effects are often small and time-limited. Incorporating a behavioral approach, such as strategy training, offers a promising avenue for improving executive functions and related stroke outcomes. Therefore, the primary aim of this study is to investigate the efficacy of strategy training for physical activity (STPA) on executive functions, as measured by the Trail Making Test (TMT) Part B and the Stroop Color-Word Test (SCW), in community-dwelling adults with poststroke cognitive impairments. Secondary aims are to examine the intervention effects of STPA on global cognition, activity, participation, and physical activity levels. To achieve these aims, we are conducting a three-arm, single-blinded, multicenter, randomized phase II clinical trial. Patients aged between 18 and 80 years, diagnosed with a stroke within the past 3 years, and presenting with cognitive impairment (Montreal Cognitive Assessment [MoCA] < 26) are recruited and randomly assigned to one of three intervention groups (STPA, physical exercise, and education) at a 1:1:1 ratio. Each group receives twelve 1-hour sessions over a maximum of 6 weeks. Primary and secondary outcomes are assessed at baseline, post-intervention, and 3-month, 6-month, and 12-month follow-ups. Due to blinding, this report focuses on recruitment progress and baseline group comparisons. Successful recruitment is defined as completion of baseline assessment and receipt of at least one intervention session. As of June 30, 2026, the recruitment rate is 45% (expected total: 120 participants). The 54 participants recruited to date (37% female; 46% ischemic stroke) have a median age of 63 years (IQR: 53–70), median time since onset of 10 months (IQR: 6–20), median MoCA score of 23 (IQR: 19–25), and median weekly physical activity of 280 metabolic equivalents of task (MET)-minutes (IQR: 66-972). Most participants experienced mild to moderate stroke, with a median National Institute of Health Stroke Scale score of 2 (IQR: 1–5) and a median modified Rankin Scale score of 3 (IQR: 2–4). Baseline characteristics and outcomes were generally comparable across groups ($P > 0.05$ based on Kruskal-Wallis or Chi-squared tests), including age, sex, MoCA, weekly MET-minutes, and executive functions (TMT Part B and SCW). However, stroke chronicity was imbalanced between groups ($P = 0.009$). Group I had a shorter median duration since stroke onset (7 months) compared with Group II (17 months) and Group III (11 months). Overall, recruitment progress has been smooth and randomization performance has been satisfactory. Nevertheless, the imbalance in chronicity requires close monitoring.

Title of Project: Impact of a Pharmacist-Led Education Program on Medication Adherence and Treatment Effectiveness of Direct Oral Anticoagulants in Patients with Atrial Fibrillation: a Randomized Control Trial

Project No.: NHRI-EX115-11409PI
P.I.: Chi-Chuan Wang/王繼娟
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2029 (Total: 5 years)

Background: Direct oral anticoagulants (DOACs) are the first-line therapy for stroke prevention in patients with atrial fibrillation (AF). Although routine monitoring of blood drug concentrations is not required with DOAC therapy, maintaining good medication adherence remains essential to achieve optimal treatment outcomes. Pharmacist-led anticoagulation clinic (ACC) services have been shown to improve adherence and clinical outcomes among patients receiving warfarin. However, evidence regarding the benefits of ACC services for patients treated with DOACs remains limited.

Objectives: To evaluate the effectiveness of pharmacist-led education on adherence and outcomes, examine DOAC use behavior through self-reported data and administrative claims data, and explore DOAC blood concentrations as an adherence biomarker. During the first two years, the project mainly focused on patient recruitment, intervention delivery, follow-up assessments, and preliminary blood concentration analyses.

Methods: A pragmatic randomized controlled trial was conducted at the National Taiwan University Hospital to evaluate the impact of pharmacist-led education and follow-up on medication adherence among patients with AF newly initiated DOACs for primary stroke prevention. Adult patients were randomly assigned to either intervention group (i.e., receiving pharmacist-led education) or control group (i.e., standard care). Follow-up assessments were conducted at 3 and 6 months after enrollment. Medication adherence and DOAC use behaviors were evaluated using the Adherence to Refills and Medications Scale, which assesses both medication-taking and refill behaviors. DOAC concentrations were measured using ultra-high-performance liquid chromatography-tandem mass spectrometry to provide an objective measure of drug exposure and explore their potential role as a biomarker of adherence.

Study progress and preliminary results: As of May 31, 2026, the study had achieved 77% of its recruitment target, with 100 of the minimum required 130 participants enrolled (54 in the ACC group and 46 in the control group). Of these, 49 participants (49.0%) completed the entire study, 16 (16.0%) remained in follow-up through month 3, and 23 (23.0%) had completed only the baseline assessment. At baseline, participants demonstrated good knowledge of most aspects of DOAC therapy, although knowledge of DOAC types was comparatively limited. Knowledge improved over time, particularly regarding DOAC types and their benefits, and was maintained throughout follow-up. Medication adherence was slightly better in the intervention group; however, this difference was not statistically significant. Notably, participants in the intervention group exhibited significantly better medication-taking behavior at the 6-month follow-up, as evidenced by lower adherence scores than those in the control group (8.6 ± 0.8 vs. 9.4 ± 1.6, $p = 0.03$, respectively). Pharmacokinetic outcomes were generally similar between groups. The proportion of ACC participants within the therapeutic range was lower than that of controls at month 3 (51.5% vs. 69.0%), whereas by month 6 this proportion was slightly higher in the intervention group (52.6% vs. 45.8%).

Conclusion: Preliminary results found participants in the ACC group demonstrated better medication adherence compared with those receiving standard care over time. The differences between adherence and pharmacokinetic outcomes requires further investigation.

Keywords: direct oral anticoagulant, pharmacist-led, patient education, medication adherence, treatment effectiveness

Title of Project: Ambient Speciated Airborne Particulate Matter on Birth Outcomes and Mortality: Collaboration with the MAIA Team of NASA

Project No.: NHRI-EX115-11410PI
P.I.: Pei-Chen Lee/李佩珍
Key Professional Personnel: Fang-Yu Kuo/郭芳妤, Ming-Tsang Wu/吳明蒼, Po-Hsiung Lin/林博雄, Chien-Cheng Jung/榮建誠, Chih-Da Wu/吳治達, Li-Te Chang/張立德, Ming-Yeng Lin/林明彥, Chia-Ni Lin/林佳霓
Affiliation/Institution: National Cheng Kung University
Entire Project Period: From 2025 to 2029 (Total: 5 years)

Background: Although outdoor particulate matter (PM) is the leading environmental risk factor for premature deaths and various diseases worldwide, many studies have focused on human exposure to the total mass of $PM_{2.5}$, whereas the relative toxicity and health effects of specific PM types remain poorly understood. The main objective of this project is to establish international collaboration with the NASA-funded MAIA (Multi-Angle Imager for Aerosols) mission/program. We assist with ground-based aerosol sampling in Taiwan, after which the collected samples are sent to the MAIA team in the United States for chemical composition analysis. These analyzed data will then be used for calibrating remote-sensing imagery.

Method: Ground-based PM composition monitoring was conducted through the SPARTAN and AMOD monitoring networks in Taiwan. Two SPARTAN monitoring sites were maintained at National Taiwan University (Taipei) and Kaohsiung Medical University (Kaohsiung). During the project period, major equipment issues, including water infiltration and pump failure, were resolved, monitoring systems were recalibrated, corroded sampler mounting structures were redesigned and replaced, and rooftop internet connectivity was upgraded to ensure stable real-time data transmission. Three AMOD samplers were deployed, including two calibration sites at National Cheng Kung University and one site at Taichung School for the Hearing Impaired. Scheduled sampling was completed successfully throughout the year, and the malfunctioning Taichung AMOD unit was replaced in collaboration with the U.S. MAIA team to maintain continuous monitoring.

Results: Complete $PM_{2.5}$ chemical composition data are currently available for 2022–2023. The average $PM_{2.5}$ concentration at the Taipei site was approximately 20 $\mu g/m^3$. $PM_{2.5}$ concentrations were generally higher in southern Taiwan than northern Taiwan and were lowest during June–August in Taipei. Sulfate was the dominant $PM_{2.5}$ component, followed by elemental carbon, while nitrate represented the smallest fraction. Compared with other MAIA monitoring sites, Taipei showed higher $PM_{2.5}$ concentrations than Rome, Atlanta, Barcelona, Los Angeles, and Boston, but lower concentrations than South Korea, Johannesburg, Santiago, Addis Ababa, and Delhi.

Current Achievements: The project has successfully established and maintained the SPARTAN and AMOD PM composition monitoring networks in Taiwan. Monitoring sites have undergone equipment upgrades, maintenance, and operational restoration to ensure continuous data collection. As a result, $PM_{2.5}$ mass concentration and chemical composition datasets have been generated for Taiwan, supporting satellite calibration and future epidemiological studies. In addition, the project has resulted in one published international collaborative research article.

Future Directions (Year 2): Future work will continue PM composition monitoring, develop historical PM composition exposure models, and establish a nationwide birth cohort for epidemiological studies.

Title of Project: Machine Learning for Physical-Mental Multimorbidity, Polypharmacy, High-Needs High-Costs Patients in Taiwan

Project No.: NHRI-EX115-11421PI
P.I.: Ta-Yu Lee/李達宇
Key Professional Personnel: Shou-Hsia Cheng/鄭守夏, Shu-Sen Chang/張書森, Charlotte Wang/王彥雯, Wan-Ju Cheng/鄭婉汝
Affiliation/Institution: National Taiwan University
Entire Project Period: From 2025 to 2028 (Total: 4 years)

Background: A small proportion of patients account for a disproportionate share of healthcare utilization and expenditure. These patients are often described as high-need, high-cost, or super high utilizers, but no universally accepted definition exists. **Objectives:** This study systematically compared multiple operational definitions of super high utilizers, including High Need (HN; CCI ≥ 4 and NCD ≥ 8, both top 5% thresholds), High Cost (HC; top 5% of annual healthcare expenditure), High Volume/High Outpatient Utilization (HV/HU; top 5% of annual outpatient visits), High Hospitalization (HH; top 5% of annual hospital admissions), and High Emergency Department Utilization (HE; top 5% of annual emergency department visits). **Methods:** We conducted a nationwide population-based cross-sectional study using the 2021 Taiwan National Health Insurance Research Database, including all continuously enrolled beneficiaries aged ≥40 years. For each definition, we examined demographic characteristics, disease profiles, healthcare utilization, and expenditure. We also assessed overlap across definitions and each group's representation in the NHI system, including shares of beneficiaries, healthcare expenditure, outpatient visits, hospital admissions, emergency department visits, and medication utilization. **Results:** Demographic and clinical characteristics differed substantially across groups. HN patients were markedly older, with 62% in the two oldest age strata compared with 25% in the overall population, and had the highest chronic disease burden, with median CCI score of 5 and median NCD count of 10. In contrast, HU, HH, and HE patients were only modestly older than the overall population and were characterized more by acute or episodic healthcare needs and greater resource use. HC patients had the highest annual healthcare expenditure, with median NT$378,772; HU patients had the most outpatient visits, with median 113 visits/year; HH patients had the most hospital admissions, with median 1 admission/year; and HE patients had the most emergency department visits, with median 5 visits/year. The definitions identified overlapping but distinct populations. In a preliminary analysis limited to HN, HC, and HV, 9.8% of the cohort met at least one criterion; among them, 31.4% met two or more definitions and 68.6% met only one. Pairwise overlap was greatest between HC and HV (N=23,945), followed by HN and HC (N=18,976) and HN and HV (N=18,294). Despite comprising only 5% of beneficiaries, HC patients accounted for 52.4% of total healthcare expenditure. HU patients accounted for 22.9% of outpatient visits, HH patients for approximately 100% of hospital admissions, and HE patients for 61.4% of emergency department visits. **Conclusions:** Super-high utilization is not a homogeneous phenomenon, but includes multiple overlapping yet distinct populations defined by clinical complexity, healthcare utilization, expenditure, and medication burden. Comparing alternative operational definitions clarifies their policy implications and helps identify appropriate targets for intervention.

Title of Project: Trends in the Prevalence and Risk Factor Control of Cardiovascular-Kidney-Metabolic Syndrome in Relation to Social Determinants of Health Among Taiwanese Adults

Project No.: NHRI-EX115-11433PI
P.I.: Hon-Yen Wu/吳泓彥
Key Professional Personnel: Hon-Yen Wu/吳泓彥, Kuo-Liong Chien/簡國龍
Affiliation/Institution: Far Eastern Memorial Hospital
Entire Project Period: From 2025 to 2027 (Total: 3 years)

Background: Cardiovascular-kidney-metabolic (CKM) syndrome is a systemic disorder characterized by the interplay among metabolic risk factors, chronic kidney disease, and cardiovascular dysfunction, resulting in multiorgan impairment and an elevated risk of adverse cardiovascular events. We examined long-term trends in the prevalence of CKM syndrome and its component diseases, together with the influence of social determinants of health (SDOH) and lifestyle behaviors on CKM syndrome among Taiwanese adults.

Methods: We analyzed adults aged ≥19 years from the 2013-2020 Nutrition and Health Survey in Taiwan, linked to National Health Insurance and death-registry data. CKM syndrome was classified into five stages (0–4) following the American Heart Association framework, and its prevalence and component diseases were assessed. All analyses incorporated the complex survey design and sampling weights. Joinpoint regression was used to estimate temporal trends, and multivariate multinomial logistic regression to evaluate associations of SDOH and lifestyle behaviors with CKM stage.

Results: Among 7,717 adults (mean age 47 years; 51% women), the overall prevalence of CKM syndrome (stages 1–4) was 82%, and was higher in men (89%) than women (74%). The prevalence was 18% for stage 0, 25% for stage 1, 45% for stage 2, 7% for stage 3, and 5% for stage 4. Component diseases were common, including dyslipidemia (60%), hypertension (42%), metabolic syndrome (29%), and diabetes (13%), and chronic kidney disease (8%). Stage 3 showed the largest increasing trend (annual percent change 2.7%; 95% confidence, 0.1% to 6.3%). Marked disparities in SDOH and lifestyle behaviors were evident across stages. Individuals without CKM syndrome (stage 0) were more likely to be women and aged <45 years, whereas those with advanced stages (3 and 4) were more likely to be men, aged ≥65 years, current or former smokers, physically inactive, and having less than secondary education. Furthermore, stage 3 was most prevalent among individuals in the lowest household income tertile and those who were separated, divorced, or widowed, whereas stage 4 was more common among the unemployed.

Conclusions: CKM syndrome is highly prevalent among Taiwanese adults, with stage 2 affecting nearly half of the population. Advanced stages are increasing, particularly among men, the elderly, smokers, physically inactive individuals, and socially disadvantaged groups—including those with lower education, lower household income, unemployment, and formerly married status. Evaluation of metabolic risk-factor awareness and control across SDOH strata is ongoing. These findings underscore the need for tailored public health strategies targeting specific SDOH and modifiable lifestyle behaviors to prevent progression to advanced CKM stages.

Title of Project: Wearable-enhanced Intervention for Elderly Depression and Sleep Disturbance - from Feasibility and Efficacy, to Development of the First Taiwanese Wearable-embedded Elderly Prospective Research Cohort
Project No.: NHRI-EX115-11516PC
P.I.: Ta-Wei Guu/谷大為
Affiliation/Institution: China Medical University Beigang Hospital
Entire Project Period: From 2026 to 2029 (Total: 4 years)

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Introduction Alzheimer's disease (AD) prevalence rises with societal ageing. In clinical care, behavioral and psychological symptoms of dementia (BPSD)—including depression, agitation/aggression, apathy, and sleep disturbance—worsen patients' quality of life and substantially increase caregiver burden, more significantly than the cognitive symptoms. Standard BPSD assessments rely on caregiver-rated questionnaires that are cross-sectional and may be biased when caregivers are themselves older adults. Device-based measures (e.g., research-grade wrist actigraphy) can provide objective longitudinal data and novel features. In parallel, therapeutic wearables may improve sleep and mood in adults, and might improve BPSD if accepted by this population.

Methods: This dyadic pilot study will recruit 20 participants (n=10 AD patients; n=10 caregivers) from outpatient services and affiliated day-care/dementia hubs in rural Taiwan. Participants will wear Geneactiv continuously for 8 weeks and Re-Timer ≥30 min/day for 4 weeks. Device-based data will be processed with GGIR, a well validated R-package designed for processing accelerometer data. Questionnaire assessments include Pittsburgh Sleep Quality Index (PSQI), Neuropsychiatry Inventory Questionnaire (NPI-Q), Caregiver Burden Inventory (CBI), and a semi-structured interview based on the Taiwanese version of Quebec User Evaluation of Satisfaction with Assistive Technology (T-QUEST) at prespecified timepoints.

Results: Ten patient-caregiver dyads were recruited successfully. In both arms, 9 patients and 9 caregivers fully adhere to the study protocol during the entire study period. The patients were predominantly female with low educational attainment (mean 5.7 years and 30% illiterate). In contrast, carers were evenly split by sex, more socioeconomically diverse, and better educated (mean 13 years). Clinically, patients exhibited moderate AD (MMSE 17.5, CASI 53.9) with notable BPSD and sleep disturbances. Wearable data indicated that patients had lower physical activity (lower ENMO and M5) and more disrupted circadian rhythms (higher IV, lower IS) compared with carers. Carers, while more active and rhythmically stable, experienced moderate caregiving burden. Patients were less active and had less stable daily rhythms than carers, indicated by a much lower sleep regularity index (SRI).

Discussion: Measurement and therapeutic wearables appear to be feasible and acceptable for both people living with moderate dementia and significant BPSD, as well as their caregivers. Metrics derived from wearables provide novel perspectives complementing questionnaire-based measurements. Confirmatory studies are needed to validate the signals derived from therapeutic wearables.

Title: A Two-Stage Probabilistic Redistribution Framework for Estimating the Burden of Antimicrobial Resistance from Garbage-Coded Mortality Data in Taiwan

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

In recent years, antimicrobial resistance (AMR) has emerged as a major global public health challenge, and Taiwan has experienced a continuous increase in the disease burden and mortality associated with antimicrobial-resistant bacterial infections. However, a considerable proportion of death certificates still record Garbage Codes (GCs) as the Underlying Cause of Death (UCD), preventing accurate identification of the true infectious causes of death. This limitation consequently affects the estimation of infectious disease mortality, Years of Life Lost (YLL), and the burden attributable to AMR.

This study proposes a two-stage probabilistic redistribution framework based on the Taiwan National Mortality Registry. In the first stage, an existing garbage code redistribution model is applied to estimate the probability distribution of potential Grouped Underlying Causes (GUCs) for each garbage-coded death. In the second stage, a probability matrix linking GUCs to the 13 infectious disease categories defined by the Global Burden of Disease (GBD) study is constructed. By integrating this matrix with the probability distributions estimated in the first stage, redistributed deaths and YLL are probabilistically assigned to the corresponding infectious disease categories. Finally, by incorporating an established pathogen attribution matrix linking infectious disease categories to antimicrobial-resistant pathogens, the proposed framework estimates the expected mortality burden and YLL attributable to specific infectious diseases and AMR-related pathogens.

By addressing the uncertainty introduced by garbage-coded deaths, the proposed framework improves the accuracy of estimating the burden of infectious diseases and AMR. It provides more comprehensive and reliable mortality surveillance and serves as an evidence-based tool for informing AMR control strategies, public health resource allocation, and burden-of-disease assessment. Furthermore, the proposed framework is highly extensible and can be readily applied to other disease classification systems and burden-of-disease studies.

Title: Development of a Taiwan-Specific FHIR-Based Template for Antimicrobial Resistance Data

P.I.: Hsiao-Hui Tsou/鄒小蕙
Presenter: Chieh Cheng/成捷
Institute/Center: National Health Research Institutes

Antimicrobial resistance is one of the top ten global health threats, making antimicrobial resistance data important for treatment and public health surveillance. However, antimicrobial resistance data are often generated across multiple laboratory procedures and recorded using different formats across healthcare institutions, limiting data interoperability and secondary use. Fast Healthcare Interoperability Resources (FHIR) is an internationally recognized standard for healthcare information exchange. This study aimed to develop a Taiwan-specific standardized data representation for antimicrobial resistance information using the FHIR framework. Common microbiology laboratory data were represented in FHIR format. International standard terminologies, including SNOMED CT and LOINC, were incorporated to support semantic interoperability. The resulting materials include an antimicrobial resistance data architecture diagram, FHIR-based JSON examples, and mapping tables linking common bacterial pathogens to SNOMED CT concepts. To our knowledge, this study represents one of the few publicly available cases in Taiwan demonstrating the application of FHIR to antimicrobial resistance data standardization. These outputs provide a structured and interoperable foundation for future clinical data exchange, antimicrobial resistance surveillance, and research applications.

Title: Economic and Epidemiologic Trade-offs of Workforce Absence During Omicron

P.I.: Hsiao-Hui Tsou/鄒小蕙
Presenter: Fang Jing Lee/李芳靚
Institute/Center: National Health Research Institutes

Pandemic response policies aim to reduce infections and prevent healthcare system overload, but interventions such as isolation and quarantine can also disrupt workforce availability and economic activity. While most studies emphasize lockdowns and demand shocks, less attention has been paid to labor-supply disruptions caused by worker absence. Taiwan's 2022 Omicron wave provides a unique case, as the country rapidly transitioned from successful containment to "living with the virus" while serving as a critical hub in global semiconductor and ICT supply chains.

To evaluate how infection- and policy-induced labor shortages propagate through production networks, we integrated a SEIRV epidemiological model with a computable general equilibrium (CGE) model calibrated using Taiwan's Social Accounting Matrix. Results indicate that under high vaccination coverage, masking remained an effective intervention, delaying the epidemic peak by 5–12 days and reducing hospital bed demand by 10–17%. In contrast, extending quarantine and isolation beyond 3–5 days provided only limited additional epidemiological benefits while substantially increasing workforce shortages.

Annual GDP losses ranged from 0.15% to 0.77%, with approximately 90% attributable to policy-mandated quarantine rather than disease severity. A 1% reduction in workforce resulted in a 0.4% decline in national output. Economic impacts were uneven across sectors, with consumption-oriented industries experiencing the greatest losses due to both direct labor shortages and value-chain spillovers. Disruptions affecting central production nodes also posed risks of cascading failures throughout the economy.

These findings suggest that pandemic strategies in highly vaccinated settings should prioritize masking and flexible quarantine policies rather than prolonged isolation. Public health planning should simultaneously protect healthcare capacity and critical production networks, recognizing resilient health systems as essential for sustaining macroeconomic stability during future outbreaks.