National Taiwan University and Academia Sinica Joint Program Office

NO. 4 Issue

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NEWSLETTER

TOPIC

The NTU/AS Innovative Joint Program has been implemented for several years, and lots of PIs achieved excellent outcomes.

In this Issue, we have 3 articles sharing the recent research results in the field of "**Medicine**".

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From Enhancer Usage to Therapeutic Insight : PER2 in EMT Regulation

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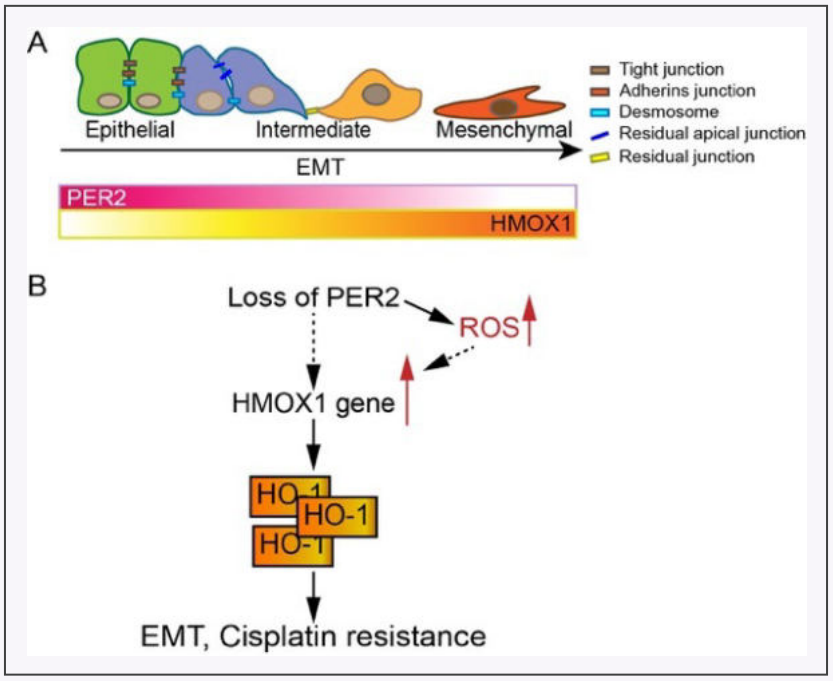
Epithelial–mesenchymal (EM) plasticity plays a central role in cancer progression, metastasis, and therapy resistance. Understanding how gene regulation contributes to cancer cell state transitions is an ongoing challenge in tumor biology. This study revealed that **distinct enhancer usage between epithelial-A (Epi-A) and mesenchymal-like (Mes-like) subtypes of ovarian cancer (OC)** underlies differential expression of key regulators of cell state. Among several candidates analyzed, the **circadian gene *PER2*** emerged as a prominent focal point for further investigation.

By integrating **Professor Ruby Huang's expertise in epithelial-mesenchymal transition (EMT)** with **Professor Wendy Hwang-Verslues' specialization in circadian biology in cancer**, the research team brought together complementary perspectives to uncover a **previously unrecognized tumor-suppressive role for the circadian gene *PER2***. This interdisciplinary collaboration established PER2 as a critical regulator in the epithelial-A (Epi-A) subtype of OC.

Professor Huang's team focused on the **epigenomic and 3D genome landscape** of the *PER2* locus. They identified subtype-specific enhancer usage differences, revealing that Epi-A OC cells maintain active enhancer elements at *PER2* that are largely inactive in Mes-like cells. These enhancer distinctions were closely linked to PER2 expression and EMT status, laying the groundwork for functional validation.



Simultaneously, Professor Hwang-Verslues' team, with deep expertise in **circadian biology and in vivo modeling**, led the mechanistic studies to evaluate PER2 function in OC. By integrating molecular, cellular, and animal model approaches, they demonstrated that **PER2 acts as a tumor suppressor** in the Epi-A subtype. High PER2 expression was associated with improved clinical outcomes, while its loss triggered EMT, increased invasiveness, and led to resistance to cisplatin treatment. Crucially, PER2 was shown to **repress the expression of HMOX1/HO-1**, a key stress response gene, and **pharmacological inhibition of HO-1** successfully reversed the malignant phenotypes resulting from PER2 depletion—defining a **PER2–HO-1 regulatory axis** with translational potential.

This well-orchestrated, cross-disciplinary effort culminated in the presentation of key findings at the **AACR Annual Meeting 2025,** through the poster *"Alternative enhancer usage of PER2 locus regulating 3D genome architecture in epithelial-mesenchymal states."* A detailed mechanistic account was also shared in the preprint ***"Loss of PERIOD2 (PER2) induces HO-1-mediated epithelial-mesenchymal transition and cisplatin resistance in Epi-A ovarian cancer."***

◆Information◆

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Joint Program Title

Alternative *PER2* (Period2) enhancer usage in epithelial ovarian cancer (OC) and the functional consequences in 3D genome structure, epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) remodeling.

Program Duration

2023.01.01 - 2024.12.31

Discovery of novel protein stabilizers: Study of their efficacy toward Pompe disease

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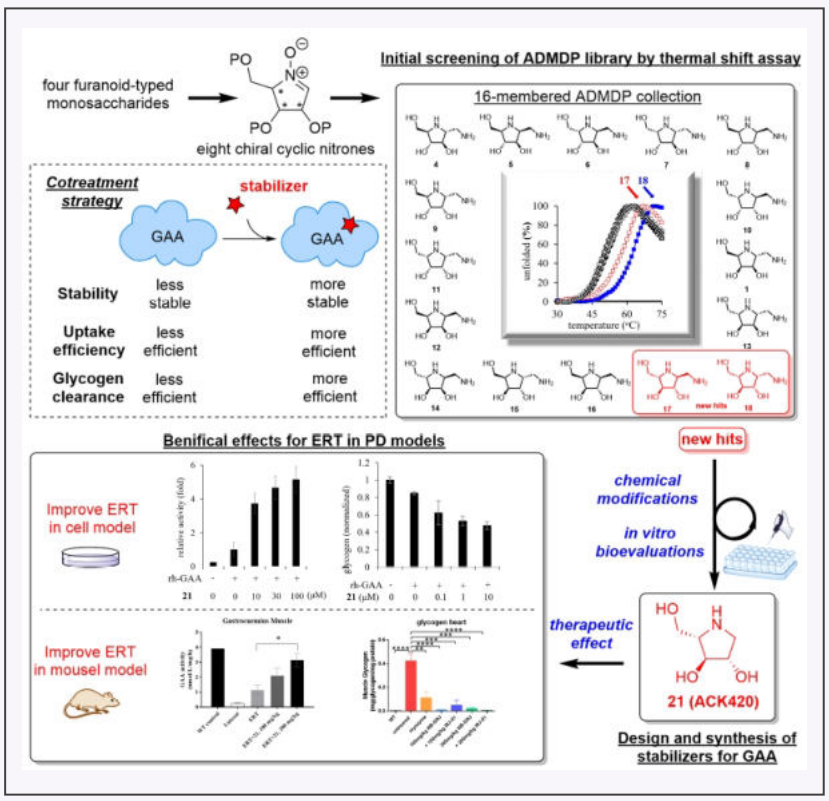
In this project, we utilized the unique polyhydroxylated pyrrolidine-based in-house chemical library consisting of all sixteen synthetic ADMDP (1-aminodeoxy-DMDP) stereoisomers (structurally covering four chiral centers, three hydroxy groups, one aminomethyl group in each stereoisomer) to study the GAA protein stability via the thermal shift assay. To our delight, two initial hits possessing the (3S,4S,5S) configuration pattern (L-arabino typed), were found. Diversification at the C2 position was performed by using natural product-inspired combinatorial chemistry (NPICC) to develop several D- and L-arabino typed iminosugars and a 300-membered amide Library.

Through our efforts, one unnatural polyhydroxylated pyrrolidine 21 was found to be the most potent and effective GAA stabilizer, suppressing GAA inactivation in enzymatic or cellular platforms. Co-treatment of 21 with rh-GAA in PD cells can not only enhance the GAA activity but also reduce the glycogen content, compared to the rh-GAA treatment (ERT) only. The durability of enzyme activity in PD cells indicated that co-treatment is able to prolong therapeutic activity and potentially amend PD patient treatment.

The enhancement effect was also found in the early proof of concept animal study, suggesting the therapeutic potential of co-treatment of 21 and rh-GAA.

We provided (1) the design, synthesis, and biological evaluation of enzyme stabilizing activity of polyhydroxylated pyrrolidines for GAA, (2) molecular modifications of polyhydroxylated pyrrolidines that lead to a significantly improved understanding of their structure-activity relationships (SAR) toward GAA stabilization , (3) computational studies that analyze the SAR of polyhydroxylated pyrrolidines toward the stabilization of GAA. These results will inspire medicinal chemists to prepare libraries with chiral diversity and the used of pyrrolidine-based iminosugars as enzyme stabilizers for other disease-associated enzymes. In this study, we emphasize the chemistry strategy instead of pharmacology-oriented study, and would like to inspire scientists to think about how to create scaffolds, molecules, and libraries as well as their structural diversity including core diversity, configuration diversity, and substituent diversity.



This is the first study to demonstrate improvements in the efficacy of enzyme replacement therapy (ERT) by adding a pyrrolidine-based small molecule into GAA in vivo, and sheds light on the discovery of pyrrolidine-based GAA stabilizers initially from the unique pyrrolidine-based natural product-inspired chemical space. We do believe our chemistry and the developing

strategy of protein stabilizers will inspire other scientists and chemists to discover other new small molecules as protein stabilizers toward other disease-associated enzymes.

This achievement was made possible through the close collaboration between the chemistry-focused team led by Wei-Chieh Cheng and the biomedical-focused team led by Wuh-Liang Hwu. Cheng's team focused on the rational design and chemical synthesis of polyhydroxylated pyrrolidine derivatives and successfully developed compound **21**, a potent stabilizer of GAA. Hwu's team conducted rigorous biological validation of ERT in disease-relevant cellular and animal models, thereby establishing the therapeutic relevance of compound **21**'s stabilizing effect. The outcomes of this collaboration have not only been published in peer-reviewed scientific journals but have also advanced to patent applications, representing a significant step forward in the development of improved therapeutic strategies for Pompe disease.

- Li HY, Lee NC, Chiu YT, Chang YW, Lin CC, Chou CL, Chien YH, Hwu WL, Cheng WC. "*Harnessing polyhydroxylated pyrrolidines as a stabilizer of acid alpha-glucosidase (GAA) to enhance the efficacy of enzyme replacement therapy in Pompe disease.*" **Bioorg Med Chem.** 2023 Jan 15 ; 78:117129

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Joint Program Title

Discovery of novel protein stabilizers: Study of their efficacy toward Pompe disease

Program Duration

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Investigation of piezoelectric stimulation for neuromodulation

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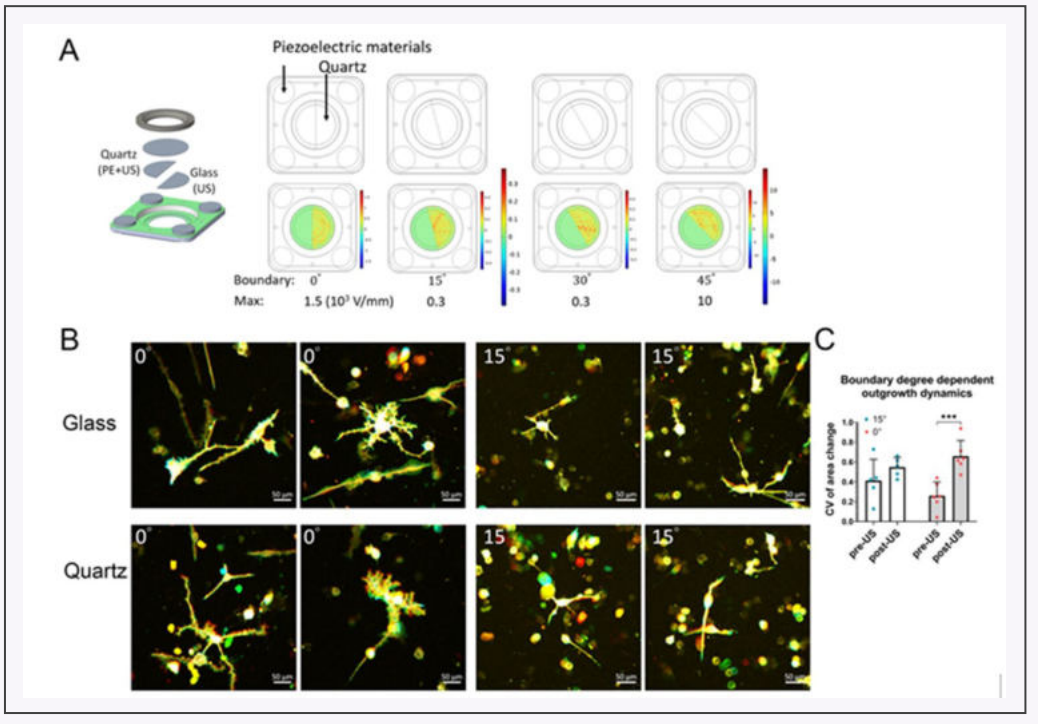
This study explores the role of piezoelectricity in physiology, in particular the influence of piezoelectric stimulation on cells in skeletal systems and neurons. The aim is to identify unique effects of piezoelectric stimulation for possible translation into clinical applications. Here we found that piezoelectric stimulation can facilitate migration and chondrogenesis of bone marrow derived stem cells. It also affects cell polarity and rearrangement of chondrocytes. All of these are relevant to bone fracture healing. In other words, piezoelectric stimulation could help facilitate fracture healing.



Based on this finding, we have proposed new projects to develop piezoelectric implants and filed several patents related to this. We expect to validate our hypothesis in animal studies as the next step. We also found that piezoelectric stimulation can influence neurite outgrowth, suggesting potential therapeutic opportunities in neuronal repair in nervous system trauma. We will continue to explore molecular mechanisms for this effect and explore the possibility for translation. The joint research teams published 6 journal articles and obtained several patents, including 2 Taiwan and 1 US patents, during the course of this project.

This research was jointly conducted by Professor Chih-Cheng Chen's team, responsible for neural cell culture and analysis, and Professor Jaw-Ling Wang's team, which developed an innovative ultrasound-coupled piezoelectric stimulation platform. By using a confocal laser scanning microscope, the research team observed in real time the responses of stimulated neural cells (e.g., growth cones). The results demonstrated the added value of interdisciplinary collaboration and promote frontier research on ultrasound and piezoelectric stimulation for neural modulation.

- Der-Sheng Han, Cheng-Han Lee, Yih-Dar Shieh, Ke-Vin Chang, Shing-Hong Lin, Ya-Chern Chu, Jaw-Lin Wang, Chih-Cheng Chen, "*Involvement of ASIC3 and Substance P in Therapeutic Ultrasound–Mediated Analgesia in Mouse Models of Fibromyalgia*." **The Journal of Pain**, Vol. 24(8), 1493-1505 , Aug 2023

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Joint Program Title

Investigation of piezoelectric stimulation for neuromodulation

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