Curriculum Vitae

Name
Yu-Yuan Hsiao (蕭育源)

Current Position
Professor / Director
Institute of Molecular Medicine and Bioengineering,
National Yang Ming Chiao Tung University (NYCU)

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Education & Professional Experiences (Times New Roman, 11 point)

2025/08 – Director, Institute of Molecular Medicine and Bioengineering, NYCU
2021/08 – Professor, Institute of Molecular Medicine and Bioengineering, NYCU
2018/08 – 2021/07 Associate Professor, Institute of Molecular Medicine and Bioengineering, NYCU
2013/08 – 2018/07 Assistant Professor, Institute of Molecular Medicine and Bioengineering, NCTU
2010/08 – 2013/07 Academia Sinica Distinguished Postdoctoral Scholar, Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan
2005/09 – 2010/06 Ph.D. National Tsing Hua University, Taiwan
2003/09 – 2005/06 M.S. National Chung Hsing University, Taiwan
1999/09 – 2003/06 B.S. Kaohsiung Medical University, Taiwan

Research Interests (Times New Roman, 11 point)

Structural biology, Nucleic acid-binding proteins, Structure-based drug discovery, Intrinsically disordered regions/proteins (IDRs/IDPs)

Selected Publications (※3-5 major papers)

1. Huang, K.W.; Tsai, C.Y.; Wu, C.Y.; Lin, W.C.; Wu, M.T. ; Hsu, K.C.; Yang, C.Y. ; Chang, I.Y.; Liu, H.M.*; Chu, J.W.*; **Hsiao, Y.Y.*** (Corresponding Author), Disordered DNA-binding Motif Forms a Modulation Site for Inhibiting the Cancer Immunotherapy Target TREX1. ***Nucleic Acids Res.***, **2026**, 54, Issue 2, https://doi.org/10.1093/nar/gkaf1511

2. Huang, K.W.; Wu, C.Y.; Toh, S.I.; Liu, T.C.; Tu, C.I; Lin, Y.H.; Cheng, A.J.; Kao, Y.T.; Chu, J.W.*; **Hsiao, Y.Y.*** (Corresponding Author), Molecular Insight into the Specific Enzymatic Properties of TREX1 Revealing the Diverse Functions in Processing RNA and DNA/RNA Hybrids. ***Nucleic Acids Res.***, **2023**, 51, Issue 21, 11927–11940, https://doi.org/10.1093/nar/gkad910

3. Huang, K.W.; Chu, Y.Y.; Hua, T.U.; Chiu, T.Y.; Liu, J.U.; Tu, C.I.; Hsu, K.C.; Chu, J.W.*; **Hsiao, Y.Y.*** (Corresponding Author), Targeted Covalent Inhibitors Allosterically

Deactivate the DEDDh Lassa Fever Virus NP Exonuclease from Alternative Distal Sites. ***J. Am. Chem. Soc. Au***, **2021**. 1, 12, 2315–2327 ; doi.org/10.1021/jacsau.1c00420

4. Liu, T.C.; Guo, K.W.; Chu, J.W.*; **Hsiao, Y.Y.*** (Corresponding Author), Understanding APE1 Cellular Functions by the Structural Preference of Exonuclease Activities. ***Comput. Struct. Biotechnol. J***. **2021**. Jun 24;19:3682-3691. doi: 10.1016/j.csbj.2021.06.036.

5. Liu, T.C.; Lin, C.T.; Chang, K.C.; Guo, K.W.; Wang, S.Y.; Chu, J.W.; **Hsiao, Y.Y.*** (Corresponding Author), APE1 distinguishes DNA substrates in exonucleolytic cleavage by induced space-filling. ***Nat Commun.*** **2021**, 12, 601. https://doi.org/10.1038/s41467-020-20853-2.

Lecture Title

Active-Site–Independent Inhibition of TREX1 Mediated by Fuzzy Interactions within a Nucleic Acid–Binding Intrinsically Disordered Loop

Abstract (500 words maximum)

As a central exonuclease in cytosolic immune regulation and nuclear DNA repair, TREX1 represents an attractive target for cancer immunotherapy. At the substrate-binding interface adjacent to its DEDDh catalytic core, TREX1 contains an intrinsically disordered region (IDR) within the α7–8 loop. Here, we identify a series of small-molecule inhibitors that engage this IDR-defined modulation site and induce distinct disorder-to-order transitions. High-resolution X-ray crystallography reveals a conserved triangular clamping mode through which the inhibitors stabilize the flexible loop into defined conformations. Structural analysis combined with molecular dynamics simulations further demonstrates that these conformational transitions arise from fuzzy interaction patterns between the IDR and the inhibitors in aqueous solution. Biochemical assays together with in vitro and in vivo functional studies show that stabilization of the loop interferes with substrate recognition and suppresses TREX1 activity by disrupting DNA binding. Targeting this IDR-mediated conformational switch thus establishes an active-site–independent strategy for TREX1 inhibition in cancer immunotherapy. Although IDRs are widespread in the mammalian proteome and offer potential for highly specific drug targeting, their disorder-to-order mechanisms remain poorly characterized due to limited structural insight. Our study provides rare atomic-level evidence of inhibitor-induced structural ordering within an IDR and advances the mechanistic understanding of IDR druggability in nucleic acid–binding proteins.