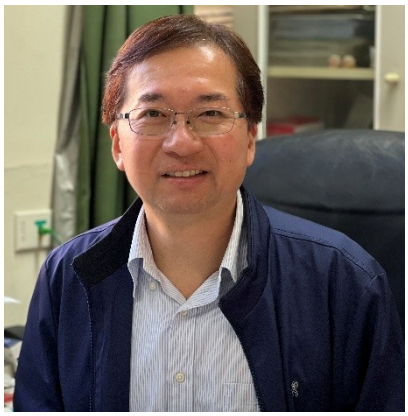
Curriculum Vitae



Name
Nei-Li Chan

Current Position
Professor
Institute of Biochemistry and Molecular Biology
National Taiwan University

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Education & Professional Experiences (Times New Roman, 11 point)
BSc, Department of Chemistry, National Taiwan University (1991)
PhD, Department of Biochemistry, University of Iowa (USA) (1998)
Associate Dean, College of Medicine, National Taiwan University (2019/08 ~ 2025/07)
President, Taiwan Biophysical Society (2022/07 ~ 2025/06)

Research Interests (Times New Roman, 11 point)
Structural biology and structure-based drug development
Structural basis of protein allosterism
Regulation of DNA topology

Selected Publications (※3-5 major papers)
1) Liu, K.-T., Chen, S.-F. and Chan, N.-L.,* (2024) Structural insights into the assembly of type II topoisomerase DNA cleavage-religation center. *Nucleic Acids Res*. doi: 10.1093/nar/gkae657
2) Tang, H., Wu, M.-H., Lin, H.-Y., Han, M.-R., Tu, Y.-H, Yang, Z.-J., Chieh, T.-C.,* Chan, N.-L.,* and Chang, W.-C.* (2022) Mechanistic analysis of carbon-carbon bond formation by deoxypodophyllotoxin synthase. *Proc. Natl. Acad. Sci*. U.S.A. 119(1):e2113770119; doi: 10.1073/pnas.2113770119)
3) Hsieh CM, Chen CY, Chern JW & Chan, N.-L.* (2020) Structure of Human Phosphodiesterase 5A1 Complexed with Avanafil Reveals Molecular Basis of Isoform Selectivity and Guide-lines for Targeting α-Helix Backbone Oxygen by Halogen Bonding. *J Med Chem*. 63:8485–8494.
4) Chen, S.-F., Huang, N.-L., Lin, J.-H., Wang, Y.-R., Wu, C.-C., Yu, Y.-J., Gilson, M.* & Chan, N.-L.* (2018) Structural Insights into the Gating of DNA Passage by the Topoisomerase II DNA-Gate. *Nature Communications*, 9(1):3085.
5) Wu, C.-C., Li, T.-K., Farh, L., Lin, L.-Y., Lin, T.-S., Chiang, C.-W., & Chan, N.-L.* (2011) Structural basis of type II topoisomerase inhibition by the anticancer drug etoposide. *Science*, 333:459-62.

Lecture Title
Crystallographic evidence for small molecule-induced disruption of a zinc-finger via covalent modification of a zinc-coordinating cysteine

Abstract (500 words maximum)
Huntington's disease (HD) is a fatal neurodegenerative disorder caused by the expression of mutant huntingtin containing pathological CAG repeat expansions. One emerging therapeutic strategy aims to selectively reduce mutant huntingtin mRNA by targeting the transcription

elongation machinery. SUPT4H, together with SUPT5H, forms a conserved complex that promotes transcription elongation across repetitive DNA sequences and has therefore attracted interest as a potential drug target. However, structural information on small molecule modulation of SUPT4H has been limited. Here we report crystallographic characterization of a small molecule inhibitor that disrupts the zinc-finger motif of human SUPT4H within the SUPT4H/SUPT5H-NGN heterodimer. High-resolution X-ray crystal structures, together with complementary assays, reveal that this compound disrupts SUPT4H zinc-finger and induces an unexpected structural rearrangement. Electron density maps show that the boronic acid moiety of the compound covalently modifies a zinc-coordinating cysteine residue (Cys36), thereby abolishing native Zn^{2+} coordination and leading to zinc-finger disruption. This observation represents, to our knowledge, the first crystallographic example of a small molecule directly targeting a zinc-coordinating cysteine to destabilize a zinc-finger fold. To further validate the proposed chemical modification, we performed soaking experiments with tetrabutylammonium fluoride (TBAF) and observed TBAF-induced restoration of zinc coordination, providing strong structural support for thioboric acid formation at Cys36. Together, these results establish a previously unrecognized mode of zinc-finger disruption and suggest a novel covalent strategy for modulating transcriptional regulators. Details of this work will be presented during the meeting.