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Thurs, 16 Oct 2025 | 3 pm | S3-05-02 Conference Room 1

Hosted by Assistant Prof Hu Chunyi

Next-Generation Discovery of Bifunctional Compounds and Molecular Glues using DNA-Encoded Libraries

By Shuang Liu

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Small molecules that induce non-native protein–protein interactions, including bifunctional compounds and molecular glues, are transforming drug discovery by enabling modulation of previously "undruggable" targets. Despite their broad therapeutic potential, systematic and efficient approaches for discovering such molecules have remained limited. Using DNA-encoded libraries (DELs) consisting of one million DNA-barcoded compounds, we discovered novel bifunctional degraders for bromodomain proteins BRD2/3/4/T, including compounds with selectivity across closely related bromodomain paralogues. Using the same DEL, we further discovered novel molecular glues between BRD9 and VHL by prioritising cooperativity in ternary complex formation. Notably, our most cooperative hit compound exhibits micromolar binding affinity to BRD9 but nanomolar affinity for the ternary complex with BRD9 and VHL, with cooperativity comparable to classical molecular glues. Together, these findings demonstrated the power of DEL screening to accelerate the discovery of both bifunctional compounds and molecular glues for preselected proteins, facilitating the transition to a new paradigm of proximity-inducing therapeutics.

About the Speaker

*Dr Shuang Liu obtained her undergraduate degree in Chemistry with Medicinal Chemistry from Imperial College London, funded by the National Science Scholarship (BS-PhD). She then joined A*STAR's Experimental Therapeutics Centre, focusing on fragment-based drug discovery. She earned her DPhil in Chemical Biology at the University of Oxford under Prof. Christopher Schofield, where she studied oncogenic variants of isocitrate dehydrogenase 1. Shuang pursued postdoctoral training with Prof. Stuart Schreiber at the Broad Institute of MIT and Harvard, where she pioneered the use of DNA-encoded library screening to discover bifunctional and molecular glue-like compounds. This work was among the first to systematically identify molecular glues using a high-throughput platform. In 2023, she returned to A*STAR IMCB to start her independent research on molecular glue discovery. Her work is supported by the A*STAR Young Achiever Award (2023) and the National Research Foundation Fellowship (2025).*