NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

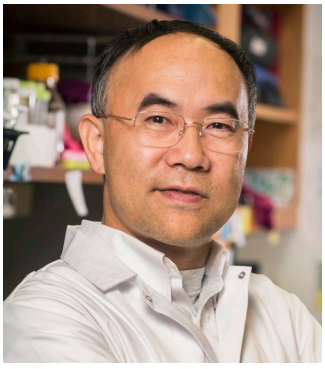
ON-SITE BIOLOGY COLLOQUIUM

Friday, 28 Feb 2025 | 4 pm | S3 05-02 Conference Room 1

Hosted by Prof Yang Daiwen

Map to Block S3

Breaking Barriers in Translational Medicine: Unlocking Undruggable Protein Interfaces and Hidden Conformations



By **Pei Zhou**
Duke University School of Medicine

Advances in structural biology and molecular modeling have revolutionized drug discovery, yet targeting hidden conformational states or disrupting macromolecular assemblies remains a challenge. We present translational research on cancer therapeutics and antibiotics addressing traditionally undruggable targets. For cancer, we identified JH-RE-06, a translesion DNA synthesis inhibitor that disrupts complex assembly by inducing target dimerization. JH-RE-06 sensitizes a variety of tumors to cisplatin and enhances enzalutamide efficacy against prostate cancer in vitro and in murine tumor models. For antibiotics, we exploited hidden ligand conformations to rapidly develop novel inhibitors of essential lipid A enzymes, LpxC and LpxH, in Gram-negative bacteria. Our lead LpxC inhibitor effectively eradicates infections caused by susceptible and multidrug-resistant Gram-negative pathogens in murine models of sepsis and soft tissue, urinary tract, and lung infections. These studies highlight the opportunities for targeting undruggable protein interfaces and hidden conformational states to address critical medical challenges.

About the Speaker

Dr. Zhou earned his B.S. from the University of Science and Technology of China in 1993 and Ph.D. from Harvard in Chemistry and Chemical Biology in 1998. He completed postdoctoral training at Harvard Medical School before joining Duke University in 2001. His research centers on macromolecular assembly and inhibition, covering areas of bacterial envelope biogenesis, host-microbe interactions, translesion DNA synthesis, metabolic signaling, and NMR methodology, with over 125 publications & 12 patents. His patent on translesion DNA synthesis inhibitors was licensed by D5 therapeutics (Korea) for commercialization. In 2015, Dr. Zhou co-founded Valanbio Therapeutics with his colleague, Dr. Eric Toone, to translate the basic research discovery of LpxC inhibitors to clinical therapeutics.