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Shaomeng Wang Drug Discovery Distinguished Lecture Series

Hosted by the
Department of Medicinal Chemistry

Molecular Glues Inspired by Natural Products as New Modulators of Protein Function

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September 17, 2026 | BSRB

Biomedical Science Research Building - ABC Seminar Rooms

Natural products have served as an invaluable source of both drugs and chemical tools for exploring a wide range of cellular processes. Rapamycin, FK506, and cyclosporin A (CsA) are macrocyclic natural products that have played important roles in unraveling cellular signaling pathways. They have also become important drugs for the treatment of organ transplant rejection, cancer, and other diseases. These macrocycles possess a unique and extraordinary mode of action—they act as molecular glues, bringing two unrelated cellular proteins together to inhibit their ultimate targets, the protein phosphatase calcineurin (CsA and FK506) and mTOR (rapamycin). Inspired by the mode of action of these natural products and their intrinsic drug-like properties, we embarked on the design and synthesis of a novel class of hybrid macrocycles known as rapafucins by replacing the mTOR-interacting effector domain of rapamycin with a combinatorial oligopeptide library. A first-generation library of 45,000 rapafucins has been synthesized and screened in a variety of cell- and target-based assays. Modulators of a wide range of protein targets, particularly those considered challenging or “undruggable”, have been identified and characterized. Rapafucins have emerged as a valuable source of novel chemical probes and promising leads for drug development.