University of Minnesota
Driven to Discover℠

Department of Chemistry
Seminar

9:45 a.m. Tuesday, Sept. 19, 2017 • 331 Smith Hall

Professor

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Inspiration from Fluorination: Chemical Biology Approaches to Probe Molecular Recognition Events in Transcription

Research interests: understanding the atomic-level details of protein-protein interactions (PPIs) with a focus on improving our knowledge of macromolecular recognition events.

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Abstract

My research program seeks to understand the atomic-level details of protein-protein interactions (PPIs) with a focus on improving our knowledge of macromolecular recognition events. The impact of such findings will aid development of new medicines to significantly improve human health. Using ^{19}F NMR, our unique contribution to this challenging field is our ability to develop new synthetic molecules, either small molecule, nanoparticle, or peptide-based to both image and disrupt harmful PPI signaling events.

Protein-protein interaction inhibitor discovery has proven difficult due to the large surface area and dynamic interfaces of proteins. To facilitate the early lead discovery rate, I will first describe a rapid protein-based ^{19}F NMR method for detecting protein-ligand interactions by screening low complexity molecules (fragments) as well as higher complexity molecules. We label the aromatic amino acids with the highly sensitive fluorine atom, due to the high conservation of aromatic residues at protein interfaces. We have tested the sensitivity, accuracy, and speed of this method with the protein interaction domain of CBP, KIX, screening 508 small molecule fragments. In the second part of the talk, I will describe improvements in our method for the field of epigenetics targeting bromodomain-containing proteins Brd4, BrdT and BPTF. These studies have led to the discovery of some of the first selective ligands for the bromodomain BPTF and new submicromolar ligands for Brd4. Finally, I will address the synthesis, development, and application of two of our new chemical probes for studying epigenetic protein function, including a new role for BPTF regulation of the oncogene, c-Myc. The speed, ease of interpretation, and low concentration of protein needed for binding experiments affords a new method to discover and characterize both native and new ligands for bromodomains and may find utility in the study of additional epigenetic “reader” domains.

Refreshments will be served prior to the seminar.