



Wednesday, September 27, 2021
4:00 P.M.

Ackert Hall, Room 120

Biochemistry
&
Molecular
Biophysics

Seminar

**Apply accurate and multi-targeting
protein cross-linking to study
amyloid/protein interactions**

Haifan Wu

Chemistry

Wichita State University



Methods for analyzing protein structures and interactions in the most native cellular environment are emerging. One important method is chemical cross-linking mass spectrometry (XL-MS), which can provide conformational restraints within proteins and protein complexes for modeling protein structures, mapping interaction interfaces, and analyzing interaction networks on a whole proteome scale both *in vitro* and *in vivo*. The chemistry behind XL-MS is the design of chemical cross-linkers. Although several commercially available cross-linkers have been widely used, it remains challenging to achieve highly diverse and accurate cross-linking simultaneously. To tackle this problem, we developed a “plant-and-cast” approach that generates cross-links between two residues in two steps: a conjugation reaction (“plant”) followed by a proximity enhanced reaction (“cast”). The rate of the first-step reaction is high and is determined by the intrinsic reactivity of the cross-linking moiety to targeted residues. Instead, the rate of the second-step reaction is intrinsically low, but it gets greatly enhanced by proximity effects, which enables targeting of otherwise inert residues, including tyrosine, serine, threonine, histidine, aspartic acid, and glutamic acid. We applied this strategy to study the interaction between amyloid β fibrils and sTREM2, which are important players in the pathogenesis of Alzheimer’s disease. By mapping the interaction interface based on cross-linking data, we identified an unusual binding interface away from the TREM2 ligand binding site.