

Title: Mixed-linkage ubiquitin chains as complex regulators of cellular signaling pathways

Authors: [Simin Rahighi](#)¹, Henry van den Bedem^{2,3}, Soichi Wakatsuki^{2,4}

Affiliations: ¹Chapman University School of Pharmacy, Irvine, CA 92618. ² Bioscience Division, SLAC National Accelerator Laboratory, Stanford University, Menlo Park, CA 94025, ³Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco CA 94158, Stanford University School of Medicine, Stanford, CA 94305.

Primary Author Email: rahighi@chapman.edu

Abstract

Ubiquitin is ubiquitously expressed in eukaryotic cells and is involved in the regulation of numerous cellular functions as a single moiety or different forms of chains. By containing more than one linkage type in a single chain, mixed-linkage ubiquitin chains constitute complex signals to regulate cellular processes. In this study, we combine x-ray crystallography, molecular dynamics simulations, and protein engineering methods to design sensors for mixed-linkage ubiquitin chains. Furthermore, we synthesize various forms and combinations of mixed-linkage ubiquitin chains using chemical ligation. The sensors will be used to identify mixed-linkage ubiquitinated proteins and cellular pathways that are regulated by these complex signals.