Supporting Information

Ligandability of E3 Ligases for Targeted Protein Degradation Applications

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Table S1. Aggregate quantified chemoproteomic data of probe-modified peptides for E3 ligases and other components of the ubiquitin proteasome machinery. We have aggregated all of our chemoproteomic data from 455 distinct experiments using the alkyne-functionalized iodoacetamide probe and the isoTOP-ABPP method first reported by Weerapana and Cravatt *et al.* [1] across various human cell line proteomes. We have quantified the total number of spectral counts for each tryptic peptide identified within each E3 ligase family member across all experiments. These include data from our research group's published papers as well as our currently unpublished studies all using the same methods described in these studies[2–17]. We have consolidated redundant probe-modified peptides as much as we can and have added the total number of spectral counts and aggregate numbers of experiments where each probe-modified peptide was identified across the 455 distinct chemoproteomic experiments.

Tab 1 shows a summary of E3 ligases and other components of the ubiquitin proteasome machinery that we searched against our ligandability database with total probe-modified peptide spectral counts and experiments for each protein, separated out by the various classes of E3 ligases.

Tabs 2-10 list the individual E3 ligases, the Uniprot ID for each E3 ligase, the probe-modified peptide sequence with the modified cysteine annotated by a "*" next to the cysteine, the cysteine number, the probe used (which is all cases is the alkyne-functionalized iodoacetamide probe abbreviated as IAyne), aggregate spectral counts for each probe-modified site, and aggregate number of experiments in which the probe-modified peptide was found.

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