Discovery of ligands for TRIM58, a novel tissue selective E3 ligase

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Redirecting E3 ligases to neo-substrates leading to their proteasomal disassembly, known as targeted protein degradation (TPD), has emerged as a promising alternative to traditional, occupancy driven pharmacology. Although the field has expanded tremendously over the last years, the choice of E3 ligases remains limited, with an almost exclusive focus on CRBN and VHL. Here, we report the discovery of novel ligands to the PRY-SPRY domain of TRIM58, a RING ligase that is specifically expressed in erythroid precursor cells. A DSF screen, followed by validation using additional biophysical methods, led to the identification of the TRIM58 ligand **TRIM-473**. A basic SAR around the chemotype was established by utilizing a competitive binding assay employing a short FP peptide probe derived from an endogenous TRIM58 substrate. The X-ray co-crystal structure of TRIM58 in complex with **TRIM-473** gave insights to the binding mode and potential exit vectors for bifunctional degrader design.