Title: Targeting extracellular and membrane proteins for degradation via lysosome targeting chimeras (LYTACs)

Abstract:

Targeted protein degradation (TPD) is a promising new therapeutic modality and a tool for probing biological pathways. Several TPD platforms have emerged over the past two decades, including PROTACs, that rely on the ubiquitin proteasome system (UPS) to induce degradation. However, the cytosolic nature of the UPS restricts the target scope to proteins with accessible cytosolic domains. To expand the scope of TPD, we have developed lysosome targeting chimeras (LYTACs) for targeting extracellular and membrane proteins for degradation. LYTACs harness endogenous lysosome targeting receptors that traffic proteins to the lysosome. By bridging the target protein with a lysosome targeting receptor, LYTACs promote lysosomal degradation of extracellular and membrane proteins.

Following the initial development of LYTACs, we have identified key genetic regulators of LYTAC activity through a genome-wide CRISPR screen, and elucidated pathways that are essential for efficient lysosomal trafficking. The findings of our study have broader implications for other therapeutics that rely on cell-surface to lysosome trafficking, such as enzyme replacement therapies, nucleic acid delivery, and antibody-drug conjugates.

In addition, we have expanded the LYTAC technology by harnessing tissue-specific lysosome targeting receptors to enable targeting distinct cell types. Finally, we are using protein design methods to generate modular de novo LYTACs.