# Chemically induced proximity for targeted protein degradation

Hojong Yoon, PhD

*Broad Institute of MIT and Harvard*
*Cambridge, MA 02142, USA*
*Email: hyoon@broadinstitute.org*

Targeted cancer therapy requires complete and sustained pharmacological inhibition of the respective target, which is often challenging to achieve due to the lack of amenable sites in non-enzyme cancer targets such as transcription factors. The clinical success of thalidomide and its analogs demonstrates that small molecules that promote targeted protein degradation can overcome this limitation, providing a new pharmacologic toolbox. Most small-molecule degraders induce new protein-protein interaction through a 'molecular glue' mechanism that bridges a ubiquitin E3 ligase and the target protein. Over 600 ubiquitin E3 ligases exist in the human proteome, allowing many points of intervention to tune their substrate specificity to degrade neo-substrates, However, directly re-wiring ubiquitin ligase to degrade target protein is still challenging in that only a handful of E3 ligases such as CRBN have been successfully repurposed for targeted protein degradation. To devise general strategies for degrader discovery, it is important to acquire a comprehensive mechanistic understanding of how chemical ligands facilitate the degradation of neo-substrates. In this presentation, I will discuss 1) general principles of targeted protein degradation[1,2], and 2) the novel mechanism of small-molecule-induced polymerization for target protein degradation[3].

References:

1) Wu T, Yoon H, Xiong Y, D.Clarke S, Nowak RP, Fischer ES. Targeted protein degradation: A powerful research tool in basic biology and target discovery (2020) ***Nat. Struct. Mol. Biol.*** 27, 605-614.
2) Faust T*, Yoon H*, Nowak RP, Donovan KA, Li Z, Cai Q, Eleuteri NA, Zhang T, Gray NS, Fischer ES. Structural complementarity facilitates E7820-mediated degradation of RBM39 by DCAF15 (2020) ***Nat. Chem. Biol.*** 16, 7-14.
3) Słabicki M*, Yoon H*, Koeppel J*, Nitsch L, Roy Burman SS, Di Genua CA, Donovan KA, Sperling AS, Hunkeler M, Tsai JM, Sharma R, Guirguis A, Zou C, Chudasama P, Gasser JA, Miller PG, Scholl C, Fröhling S, Nowak RP, Fischer ES, Ebert BL. Small-molecule-induced polymerization triggers degradation of BCL6 (2020) ***Nature*** 588, 164-168.