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Ubiquitin-proteasome drug development with SNIPER technology

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Development of potent inhibitors against disease-related proteins, such as oncogenic kinases, is a promising approach for novel drug discovery. However, it is hard to develop effective inhibitors against intracellular proteins without enzymatic activity. These proteins are sometimes called "undruggable proteins", and account for approximately more than 70 % of the proteins expressed in cells. Inducing protein degradation by small molecules is a novel technology that can be applied to target the undruggable proteins. We and others have developed chimeric degrader molecules named PROTACs (Proteolysis-Targeting Chimeras) and SNIPERs (Specific and Nongenetic IAP-dependent Protein Erasers) that induce degradation of the target proteins in a highly selective manner. These chimeric molecules contain a target-ligand linked to a ligand for E3 ubiquitin ligases such as $CRL2^{VHL}$, $CRL4^{CRBN}$ and IAPs, and they induce poly-ubiquitylation and proteasomal degradation of the target proteins. Substitution of the target-ligand allows us to rationally design a novel degrader molecule against protein of interest. In the lecture, I would like to show data of our SNIPER compounds and discuss the future prospect of the protein degraders.