Small Molecule Induced Protein Degradation as an Novel Therapeutic Strategy

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Small molecule drugs are mainly restricted to functional proteins like receptors or enzymes and are therefore limited to only a fraction of the proteome. Their pharmacology model is based on the idea that the longer a drug occupies and blocks an active site, the greater the clinical benefit is. Consequently, a high local drug dosing is permanently needed to allow for therapeutic efficacy resulting in undesired side effects. Alternatively, the protein function can be blocked by removing the protein from the system. This has been achieved by nucleic acid-based strategies which prove highly effective *in vitro* but show only low bioavailability. A promising approach called PROteolysis-TArgeting Chimeras (PROTACs) combines the advantageous drug-like properties of small molecules and the modulation of intracellular protein levels by genetic knockdown techniques. Based on an "*event-driven*" paradigm, PROTACs represent a novel technology to irreversibly inhibit protein function, by selectively inducing proteolytic degradation of their protein targets and thereby irreversibly inhibiting protein function via target destruction.

PROTACs comprise bifunctional molecules capable of recruiting target proteins to the cellular ubiquitin proteasome system (UPS) thus leading to their degradation. Thus far, a variety of different target proteins have succumbed to PROTAC mediated protein degradation such as kinases, transcription factors and epigenetic readers. The catalytic nature of PROTACs allows for a drastically reduced dosage compared to traditional small molecule inhibitors with some PROTACs being already effective at picomolar concentration. Moreover, PROTAC induced protein degradation has been achieved using different E3 ubiquitin ligases including VHL (von Hippel-Lindau), MDM2 and cereblon.