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"Exploiting $CRL4^{CRBN}$ E-3 ligases for cancer drug discovery"

Manipulation of the ubiquitin–proteasome system to achieve targeted degradation of proteins within cells using chemical tools and drugs has the potential to transform pharmacological and therapeutic approaches in cancer and other diseases. Thalidomide and its analogues lenalidomide and pomalidomide exert their mechanism of action through the modulation of the $CRL4^{CRBN}$ E3 ligase family. Binding of the thalidomide to analogues Cereblon (CRBN) results in the degradation of neomorphic protein such as Aiolos and iKaros, in multiple myeloma. This degradation explains the anti-tumor activity as well as the immuno-modulatory effects of these drugs. The degradation of multiple context-specific proteins by the thalidomide analogues provides a means to uncover new cell biology as well as generate future drug molecules against currently undruggable targets. In parallel, the development of larger bifunctional molecules that bring together highly specific protein targets in complexes with cereblon, von Hippel-Lindau or other E3 ligases to promote ubiquitin-dependent degradation has progressed to generate selective chemical compounds with potent effects in cells and *in vivo* models, providing valuable tools for biological target validation and with future potential for therapeutic use. This presentation will survey recent breakthroughs achieved in these two complementary methods, with a greater focus of $CRL4^{CRBN}$ modulation.