

Selecting DNA encoded small molecules that direct protein ubiquitination

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Although using DNA encoded libraries (DELs) to find small molecule binders of target proteins is well-established, identifying DEL hits for functions other than binding remains challenging. We demonstrate here a technique where DNA-linked small molecules can be selected based on their ability to catalyze the transfer of ubiquitin (Ub) to target proteins. Since the transfer of Ub is the first step in the tagging of proteins for proteasomal destruction, finding small molecules that can selectively reprogram Ub-transfer is one of the great challenges in contemporary drug development. Our work provides the framework for applying DEL technology to the discovery of small molecules for target protein degradation.