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Nothing Degrading about Saving Lives: E3 Ligands Recruiting New Drugs

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Abstracts

REPORT INCLUDES:

An overview of E3 ligases, which have been long regarded as “undruggable targets”. Despite these failures both scientifically and financially, humiliations did not fully disrupt intense research efforts which persisted, due to the enormous potential upside

Discussion of underexploited strategies, traditional approaches that can be optimized, and novel techniques beginning to emerge and pay dividends

Information on the results propelling this field toward better clinical outcomes and insight into the Targeted Protein Degradation (TPD) which is renewing optimism in what was at one stage a field drowning in garbage proteins. Activity in the clinic is now being closely watched by the industry

REPORT HIGHLIGHTS:

Posttranslational modifications hit prime time in the pharma industry. There probably isn’t a medium sized biopharmaceutical that does not have an active program ongoing, and certainly all of the big pharma companies are running multiple programs, and collaborations, for what we might have previously termed “undruggable targets”. Many of these are for highly unmet needs in neurodegeneration.

The properties of the structure that forms between a target, a degrader and an E3 ligase, are under intense investigation. Minor changes affect how the drugs work - this

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can explain how promiscuous target-binding payloads can achieve super selectivity when transformed into a degrader. These minor alterations can also render the molecule complex not only ineffective, but sometimes toxic.

However, clinical results are beginning to write a compellingly effective story – the long and winding history of research into the ubiquitin proteasome may well have more blockbusters in store for us. And cures in a once overlooked corner of the cell machinery architecture.

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