Targeted Protein Degradation: Unlocking the Therapeutic Proteome

A novel approach to target and dispose of troublesome proteins is creating huge interest in the drug development industry. The emerging modality, known as targeted protein degradation (TPD), uses a bifunctional chemistry to create chimeric molecules that bind to a protein of interest while simultaneously tagging it for degradation via the cell’s own proteolytic machinery. This represents an entirely new rationale in the way proteins are targeted; instead of relying on small molecules that bind to druggable targets such as enzymes, ion channels and receptors (representing 10–15% of cellular proteins), TPD offers a unique means to unlock the remainder of the proteome, including previously “undruggable” proteins such as transcription factors and scaffolding molecules.

Most proteins in the body undergo degradation, either as part of their normal turnover or if they become misfolded. These proteins get tagged with a small regulatory protein called ubiquitin by a class of enzyme called E3 ubiquitin ligases. Ubiquitinated proteins unfold and are fed into a multunit channel called the proteasome that cuts them up like a molecular chipper. By co-opting the endogenous ubiquitin-proteasome machinery, proteins that are contributing to a disease process can be permanently removed. In practice, engineering bifunctional molecules that can effectively bind a protein target AND an E3 ubiquitin ligase in sufficient proximity is not trivial. The rules of this process are still being understood and often combine prior knowledge of a protein’s structure and function with high throughput chemical platforms. Proteins of interest (the protein to be degraded and the E3 ubiquitin ligase) are interrogated with small molecule libraries to identify binders that can then be joined in such a way that a permissive complex is formed, enabling ubiquitination of the target protein.

It is hoped that synthesizing promising TPDs will be facilitated by collaborating with chemoproteomics experts. Novartis has recently announced the formation of the Novartis-Berkeley Center for Proteomics and Chemistry Technologies that will leverage expertise at the university to identify chemical candidates. Boehringer Ingelheim have a similar pact with the University of Dundee where the MRC Protein Phosphorylation and Ubiquitination Unit and the FingerPrint Proteomics Facility reside. This can be a frustrating process, but when utilized successfully, TPD has shown much preclinical potential with the number of publications reporting degradation of disease-related proteins growing daily. Promising therapeutic targets include the androgen receptor for castration-resistant prostate cancer, the serine/threonine kinase TANK-binding kinase 1 (TBK1) for mutant K-Ras cancers, the transcription factors Ikaros and Aiolos for systemic lupus erythematosus and relapsed/refractory multiple myeloma, and BET bromodomain proteins for multiple cancers and adipogenesis.

Traditional pharmacological approaches rely on a drug competing against endogenous ligands for a specified site, which depends on its binding affinity and concentration. In theory, targeted degraders can bind to any region of a target protein as it does not compete with a ligand. Furthermore, because ubiquitination is a catalytic process, the TPD molecule will keep working until all of the target protein is eliminated. These attributes are extremely appealing and many pharmaceutical companies have staked their interest by investing in partnerships to develop TPD molecules that are hoped to treat a slew of previously untouchable diseases. In the last 6 months alone, Celgene Ltd. will reportedly pay the start-up Vividion Therapeutics $101 million over 4 years to develop small molecule drugs to treat cancer, inflammation and neurodegenerative diseases; Pfizer have teamed up with Avisina in a TPD discovery program worth up to $830 million, and Kymera Therapeutics has launched a TPD program with $30 million funding from Atlas Venture, Lilly Ventures, and Amgen Ventures.

Jay Bradner, formerly of the Dana-Faber Cancer Institute, co-founder of the TPD startup C4 Therapeutics, and now President of Novartis Institutes for BioMedical Research (Cambridge, USA), is one of the pioneers of the TPD field and has played an integral role in translating this modality from an academic curiosity in the early 2000s to present day pharmaceutical embrace. At the 2017 American Society of Hematology Presidential Symposium, Bradner gave a compelling talk about the potential of TPD to treat disease by targeting intractable proteins. Frustrated by the inadequate drugs available to tackle his father’s pancreatic cancer, he set out to find a better way to treat malignancies. In his seminal 2015 Science paper, he directed a chimeric protein degrader against the transcriptional co-activator BRD4 (a regulator of key oncoproteins such as c-myc, bcl-xL and bcl-6). Its proteolysis induced apoptosis of primary human acute myeloid leukaemia cells in culture and attenuated tumor progression in a human leukaemia xenograft model, demonstrating the translational potential of this technique. Various classes of TPD compound have now been created including PROTACs (PROteolysis Targeting Chimeras) and SNIPERS (Specific and Nongenetic IAP-dependent Protein Erasers). Beyond their exotic names and slightly different chemistries, the approach is essentially identical: to bring a target protein close enough to a ubiquitin ligase to elicit its proteolysis.

Although TPDs bypass many of the drawbacks of small molecular drugs, they also have associated challenges that need addressing. One concern is understanding the biological consequence of effectively knocking-out a protein from a cell that might well have multiple functions. A recent study, published in Cell on March 15, 2018, used a mass-spectrometry approach to analyze the consequences of protein degradation in biological systems. This kind of study may help to ascertain the therapeutic viability of a particular protein degrader, so unintended side-effects are understood and limited. A further challenge is finding ways to deal with the sheer size of these bifunctional molecules, and the impact this has on metabolic stability and delivery routes. The size of small molecule inhibitors is typically in the range of 300-
500 Da, while TPDs range from 700 to 1000 Da. One concern is that this might affect the oral availability of TPDs – one of the most desirable properties in drug design. Both AstraZeneca and Genentech have developed oral formulations of selective estrogen receptor degraders (SERDs) to treat estrogen receptor-positive breast cancer, and they are currently recruiting patients to enter Phase 1 trials. While highly effective at degrading estrogen receptor and blocking tumor growth in preclinical studies, these pioneering trials will determine their clinical feasibility. The results will be eagerly awaited as their success, or failure, might well influence how upcoming TPD trials will be tackled, and the extent of future investment in this nascent technology.

Using TPD agents to target and destroy disease-related proteins may be an elegant solution to the current bottle-neck faced by the drug development industry. This new generation of drugs offer the potential to harness the entire proteome so that therapeutic handles can be identified and exploited to treat previously incurable diseases. If successful, perhaps “undruggable target” will become a term of the past.