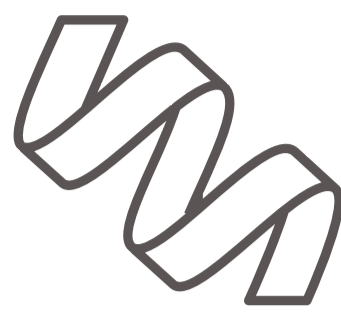


Understanding Targeted Protein Degradation

Proteins are fundamental to cellular function

Proteins are large, complex molecules that have a range of significant roles in the body and are necessary for the structure, function and regulation of tissues and organs.¹

Cells maintain the proper balance of proteins by regulating several fundamental processes including protein synthesis and degradation, or the creation and removal of proteins.²



Protein homeostasis is critical for cell health

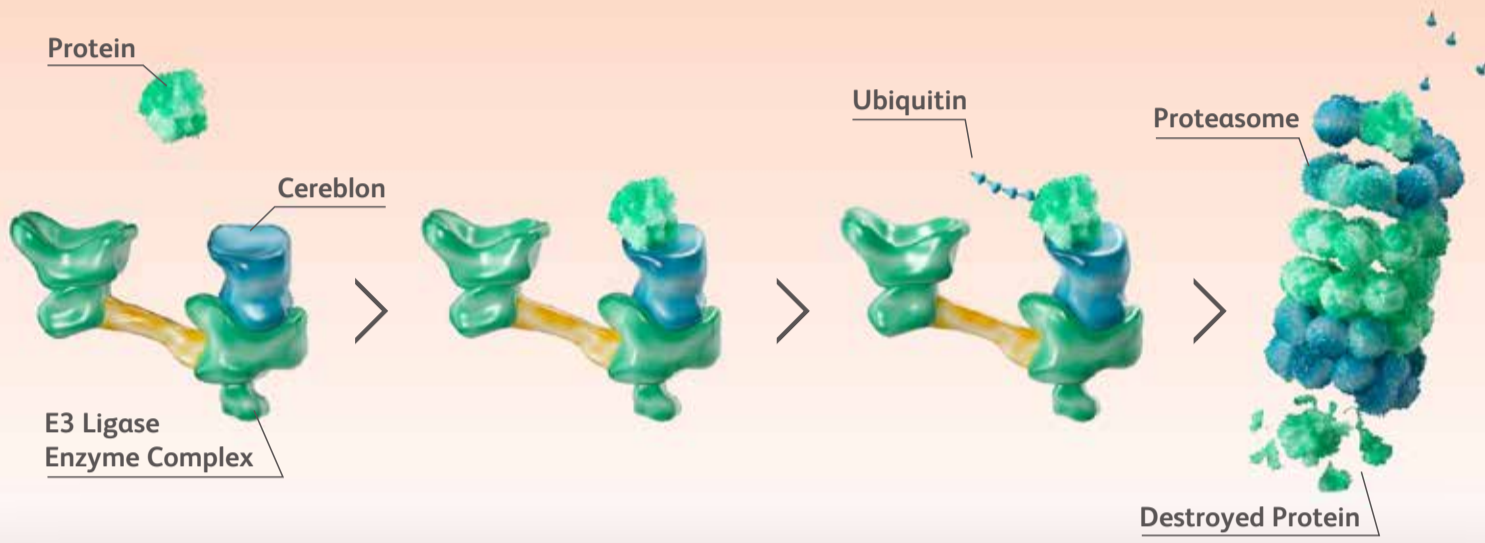
Protein degradation is part of a cell's protein homeostasis regulatory network that ensures unnecessary proteins are removed from the cellular environment when they are no longer needed or are damaged or faulty in some way.^{2,3}

An efficiently functioning proteome, or all the possible proteins in an organism, is fundamental to all cellular processes and critical to the health of the cell and lifespan of the organism.



Protein Degradation in Practice

The ubiquitin-proteasome system (UPS) is one of 2 primary means of protein degradation in cells (the other is lysosomal proteolysis). The UPS tags intracellular proteins for degradation with a small protein called ubiquitin by the E3 ligase enzyme complex. Ubiquitin-tagged proteins are then sent to the proteasome and degraded.³



The accumulation of proteins in a cell may lead to detrimental effects

When a cell is unable to degrade abnormal and/or unnecessary proteins, these proteins can accumulate within the cellular environment. The accumulation of proteins within a cell is implicated in the pathogenesis of many diseases, including several malignancies and neurodegenerative disorders.^{2,3}

Targeting a cell's protein degradation system

Many current approaches to treating cancer focus on inhibiting specific pathways or proteins.



Only up to **10%** of all human proteins are traditionally considered targetable or “druggable” given their cellular location and/or structural limitations.^{4,5}



Scientists are exploring how to use protein degradation to approach cancer research in a new way—effectively leveraging the body's natural system to target and remove the pathogenic proteins and maintain homeostasis.

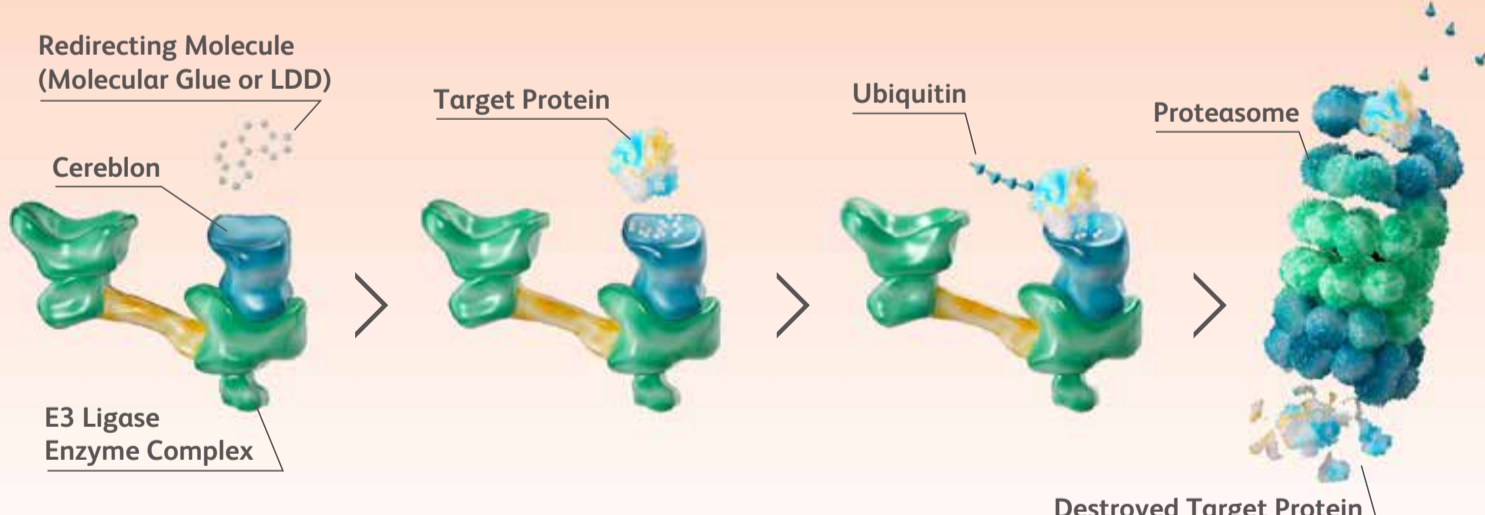


By redirecting the UPS within a cell through the introduction of protein degradation agents, scientists may be able to target thousands of previously “undruggable” proteins or proteins that are chemically intractable by direct pharmacology.⁶⁻¹³

Two Approaches to Targeted Protein Degradation

Scientists are exploring 2 approaches to promote the degradation of target proteins that would not otherwise be degraded by using 2 different types of redirecting molecules: **molecular glues** and **heterobifunctional agents** (also called **ligand-directed degraders**, or **LDDs**).

Both approaches bring the E3 ligase and the intended target protein into close proximity with each other to initiate protein degradation by the cell's UPS.



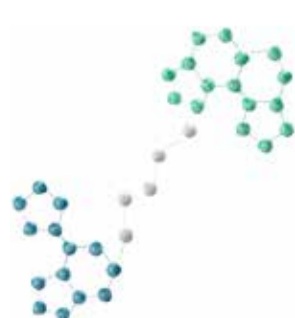
Molecular glues and LDDs work in different ways to redirect the UPS and initiate target protein degradation



Molecular Glues

Molecules that alter the protein-binding properties of cereblon (an important component of the E3 ligase) to promote interaction with and degradation of target proteins

Work by binding to a pocket on cereblon and altering its surface, changing what cereblon is able to “stick to”^{14,15}



LDDs

Three-part molecules (2 different ends joined by a linker) that redirect the UPS to degrade target proteins

Engineered to link target proteins with the E3 ligase¹⁶

Bristol Myers Squibb is building on its legacy and scientific expertise to advance the field of protein degradation and transform patient outcomes in diseases with serious unmet need, such as cancer and lupus.

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