
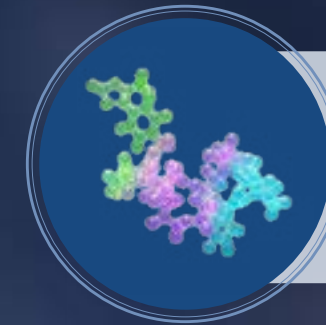

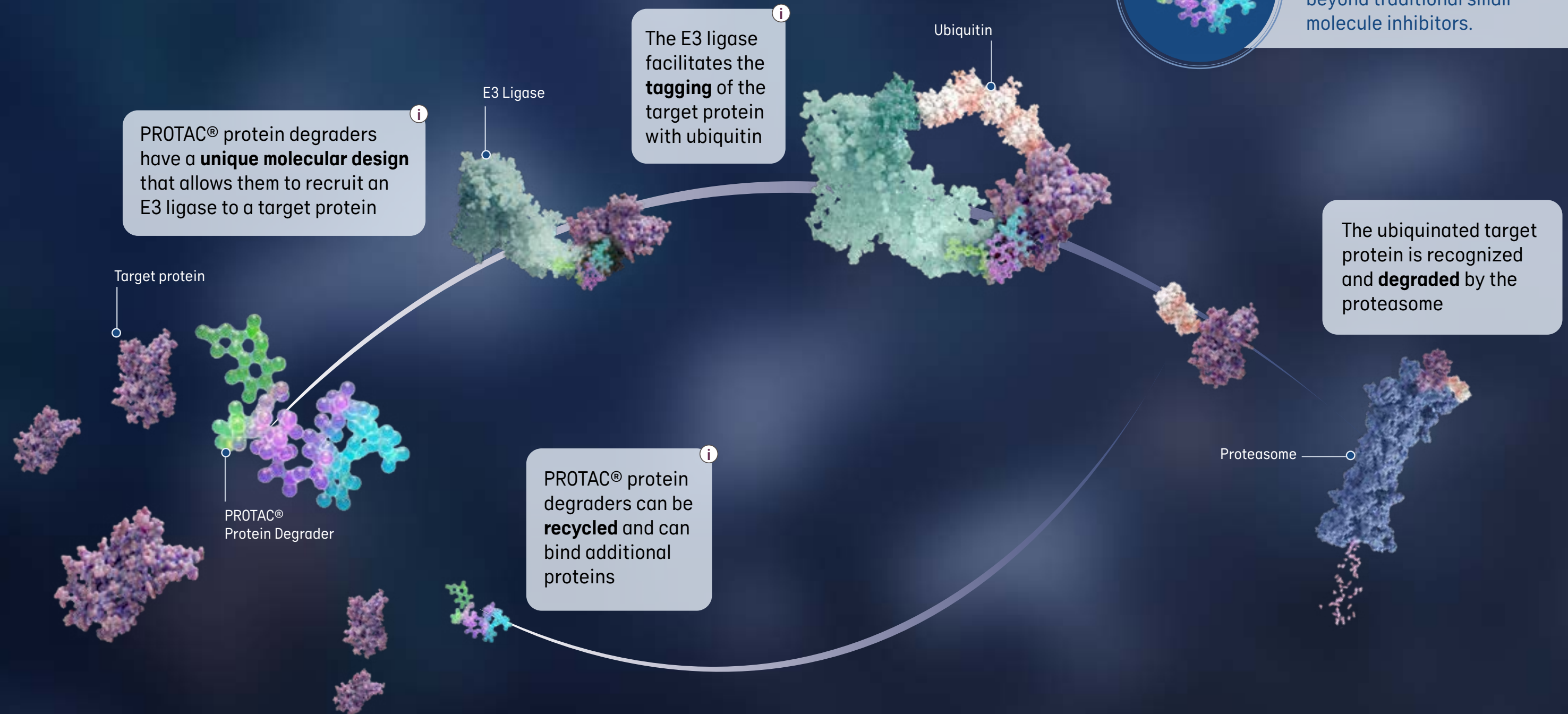


THE SCIENCE BEHIND PROTAC[®] PROTEIN DEGRADERS

Directly targeting disease-causing proteins and inducing their elimination by harnessing the body's natural protein disposal system—the ubiquitin-proteasome system. 



PROTAC[®] protein degraders have many potential applications beyond traditional small molecule inhibitors. 



THE SCIENCE BEHIND

PROTAC

The UPS—A Natural Protein Disposal System

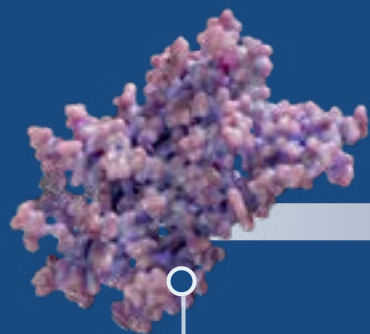
Directly targeting
the body's natural



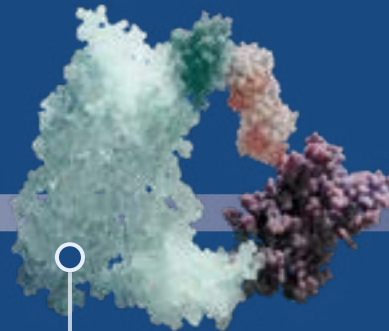
The ubiquitin-proteasome system (UPS) is involved in many basic cellular processes, including regulation of

- Cell cycle
- Immune and inflammatory responses
- Signaling pathways
- Development and differentiation

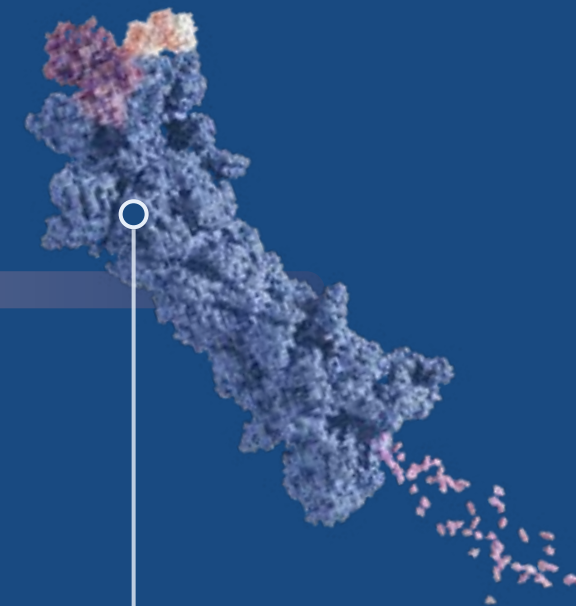
The UPS induces **DEGRADATION OF DAMAGED OR UNNEEDED PROTEINS**



Protein
Misfolded,
damaged, or
unnneeded



E3 Ligase
Facilitates ubiquitin
tagging and formation of
a chain on the protein



Proteasome
Recognizes
ubiquitinated protein
and then degrades it

See how a PROTAC® protein degrader is uniquely designed to harness the UPS



THE SCIENCE BEHIND PROTAC® PROTEIN DEGRADERS

Directly targeting disease-causing proteins and inducing their elimination by harnessing the body's natural ubiquitin-proteasome system.

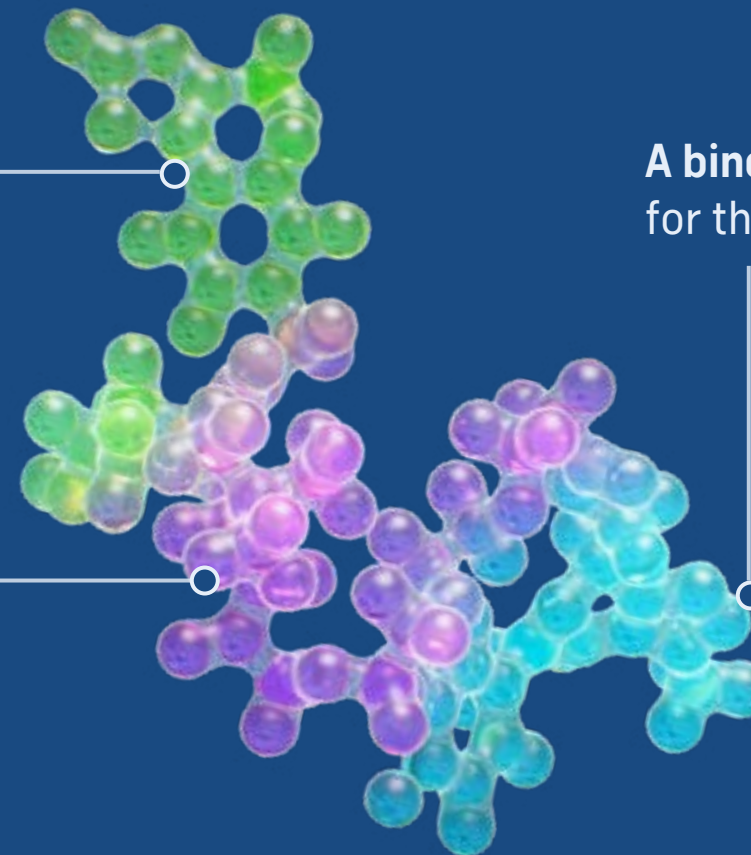
Unique Molecular Design

A PROTAC® protein degrader is a uniquely designed small molecule composed of three parts

A binding domain
for the specific E3 ligase

A linker
that connects and
positions the two domains

A binding domain
for the target protein



See how this design facilitates
targeted protein degradation

THE SCIENCE BEHIND PROTAC[®] PROTEIN DEGRADERS

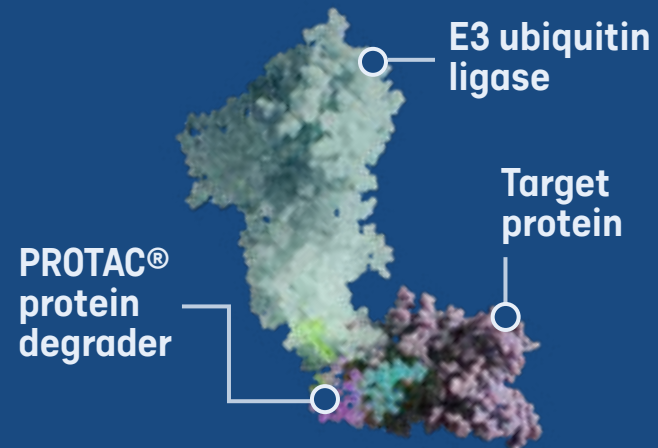
Directly targeting disease-causing proteins and inducing their elimination by harnessing the body's natural ubiquitin-proteasome system.

Targeted Protein Degradation

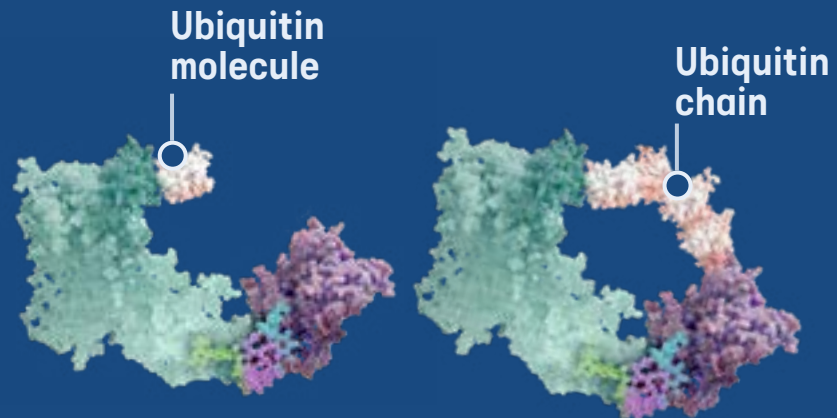
PROTAC[®] protein degraders directly induce the ubiquitin-proteasome system (UPS) to eliminate the target protein.

Recruitment of the UPS

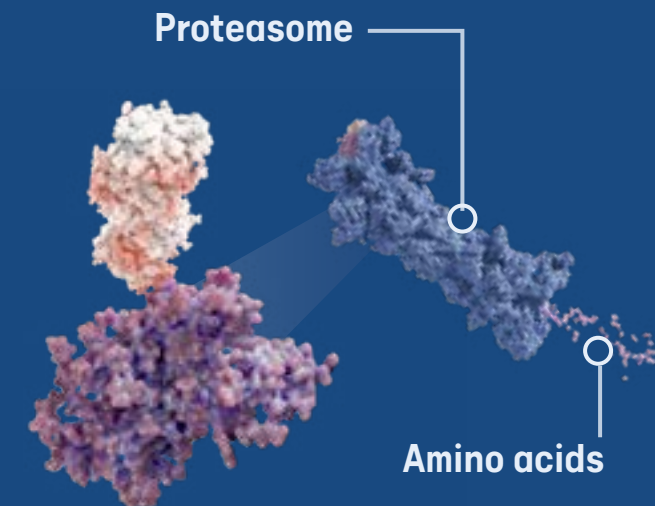
- 1 Ternary Complex**
The unique design results in the formation of a ternary complex consisting of the PROTAC[®] molecule, the target protein and the E3 ligase



- 2 Ubiquitin Tagging**
The complex triggers the E3 ligase to facilitate the transfer of ubiquitin molecules to the target protein to form a chain



- 3 Degradation**
The ubiquitinated target protein will be directed to the proteasome where it is subsequently degraded



See how this process repeats

graders
applications
mall

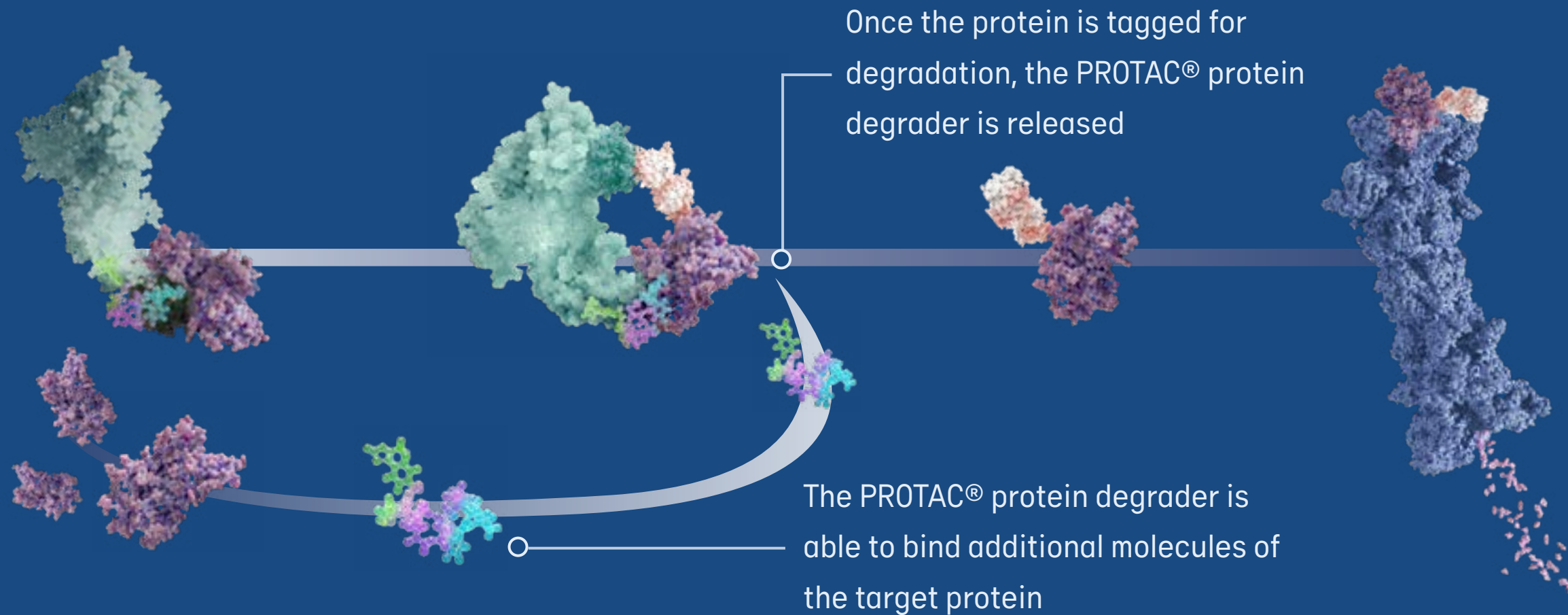
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THE SCIENCE BEHIND PROTAC® PROTEIN DEGRADERS

Repeat Degradation

Directly targeting
the body's natural

The unique iterative activity of the PROTAC® protein degrader allows for repeat degradation events.



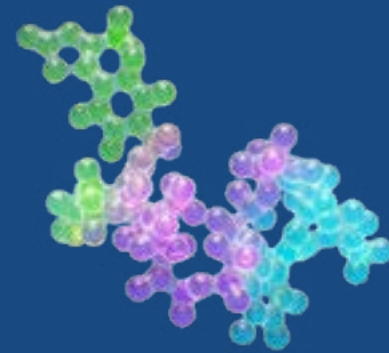
A single PROTAC® degrader molecule is able to induce tagging and subsequent degradation of multiple molecules of the target protein—up to hundreds of times.

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THE SCIENCE BEHIND PROTAC® PROTEIN DEGRADERS

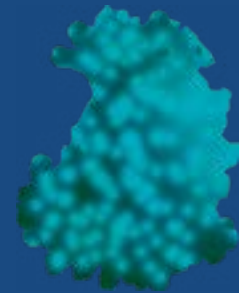
Directly targeting disease-causing proteins by leveraging the body's natural protein degradation pathway.



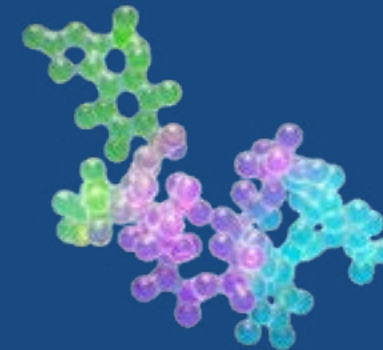
The PROTAC® Protein Degradation Difference

PROTAC® protein degraders can be developed to target multiple types of disease-causing proteins, including those that were previously considered undruggable due to a lack of a suitable active site or due to competitive inhibition.

PROTAC® Protein Degradation have many potential applications beyond traditional small molecule inhibitors.



Traditional Small Molecule Inhibitors



PROTAC® Protein Degradation

Typically inhibit enzymatic functions	Eliminate the target protein and its functions
Require an active or allosteric site for binding	Do not need to bind an active or allosteric site for target protein elimination
Require tight and often prolonged binding	Do not require tight and prolonged binding and therefore may eliminate target proteins after only weak and transient interactions
Typically do not have an iterative mechanism	Have iterative mechanism of action that allows for removal of target proteins regardless of protein levels

PROTAC® protein degraders have many potential applications beyond traditional small molecule inhibitors.

PROTAC® protein degraders have a **unique** mechanism of action that allows them to recruit E3 ligase to a target protein.

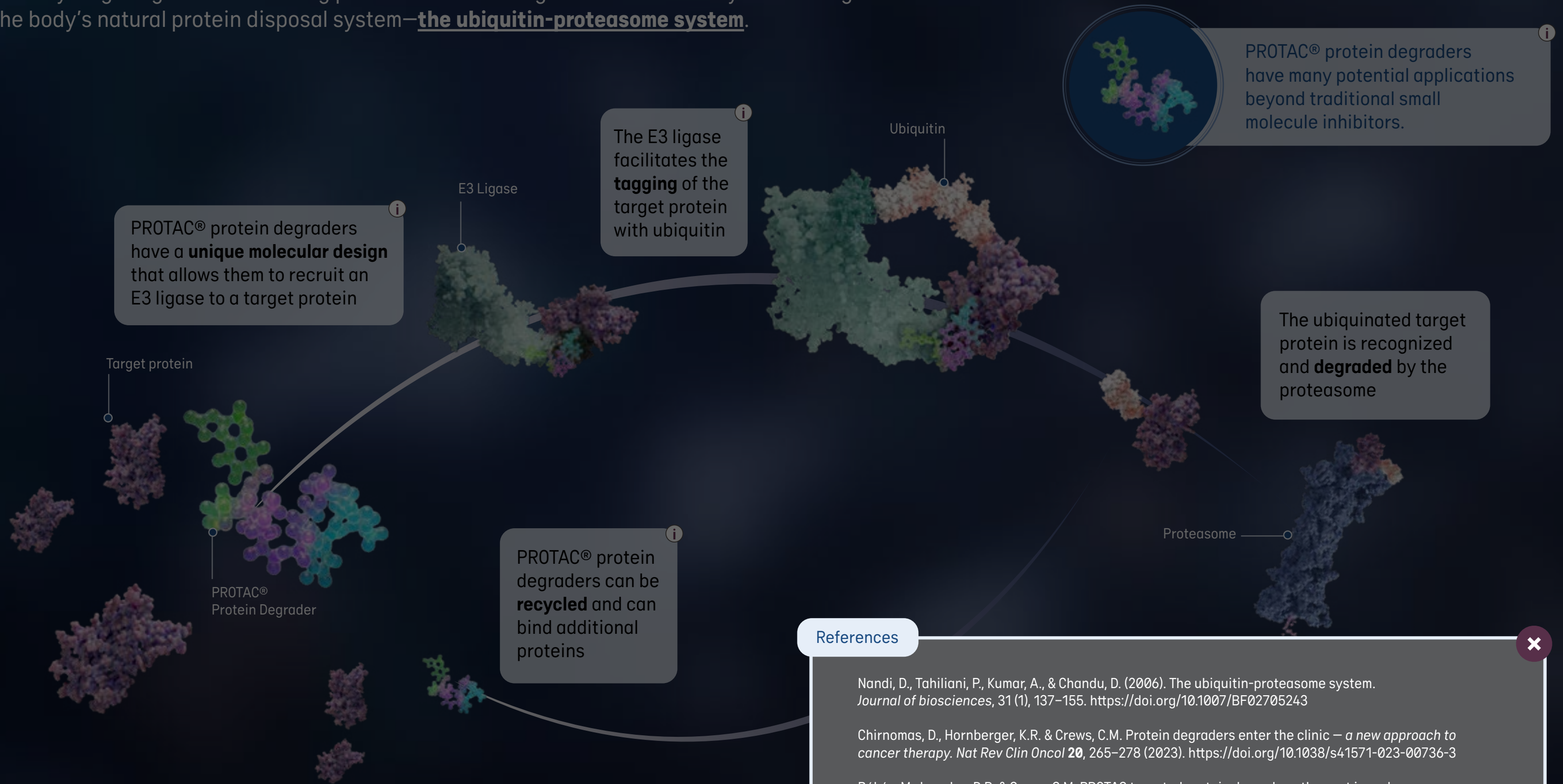
Target protein

PROTAC® Protein Degradation

The ubiquitinated target protein is recognized and **degraded** by the proteasome.

THE SCIENCE BEHIND PROTAC[®] PROTEIN DEGRADERS

Directly targeting disease-causing proteins and inducing their elimination by harnessing the body's natural protein disposal system—the ubiquitin-proteasome system.



References

Nandi, D., Tahiliani, P., Kumar, A., & Chandu, D. (2006). The ubiquitin-proteasome system. *Journal of biosciences*, 31 (1), 137–155. <https://doi.org/10.1007/BF02705243>

Chirnomas, D., Hornberger, K.R. & Crews, C.M. Protein degraders enter the clinic — a new approach to cancer therapy. *Nat Rev Clin Oncol* **20**, 265–278 (2023). <https://doi.org/10.1038/s41571-023-00736-3>

Békés, M., Langley, D.R. & Crews, C.M. PROTAC targeted protein degraders: the past is prologue. *Nat Rev Drug Discov* **21**, 181–200 (2022). <https://doi.org/10.1038/s41573-021-00371-6>