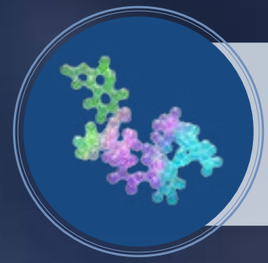
THE SCIENCE BEHIND PROTAC PROTEIN DEGRADERS

Designed to directly target disease-causing proteins and induce their elimination by harnessing the body's natural protein disposal system—**the ubiquitin-proteasome system**.



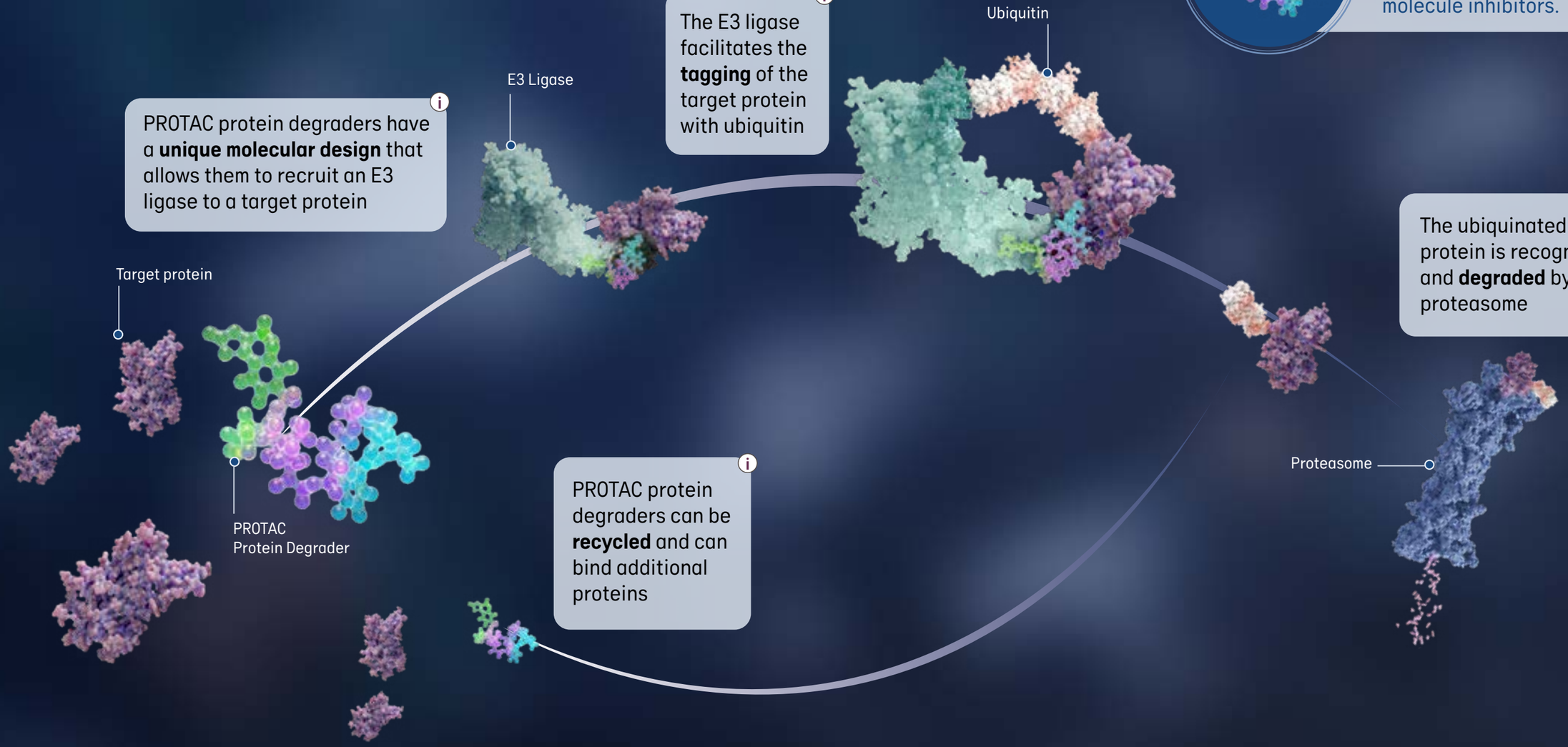
PROTAC protein degraders have many potential applications beyond traditional small molecule inhibitors.

PROTAC protein degraders have a **unique molecular design** that allows them to recruit an E3 ligase to a target protein

The E3 ligase facilitates the **tagging** of the target protein with ubiquitin

The ubiquinated target protein is recognized and **degraded** by the proteasome

PROTAC protein degraders can be **recycled** and can bind additional proteins



REFERENCES

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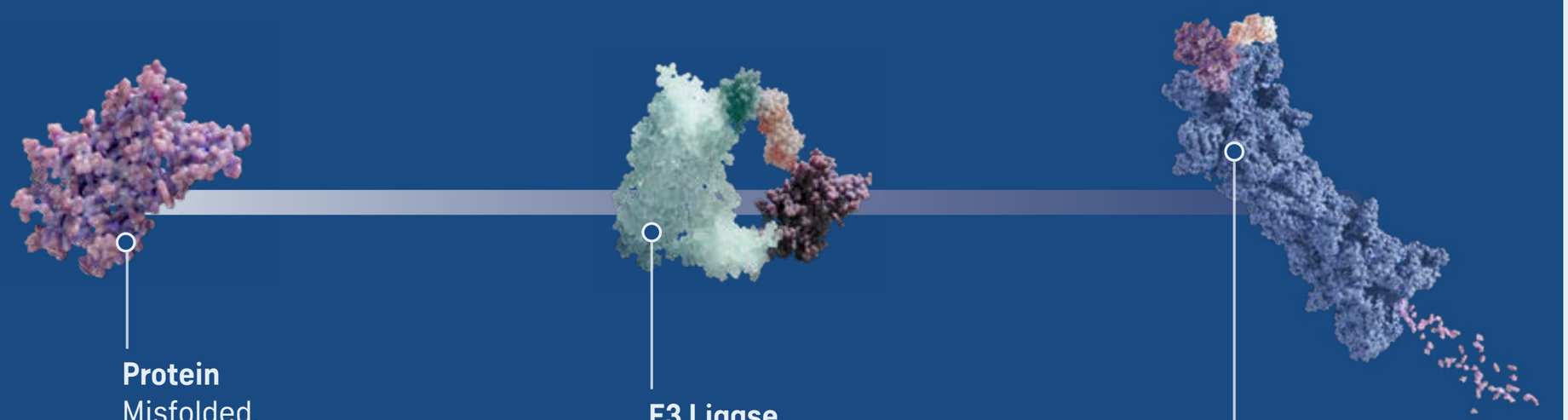
The UPS—A Natural Protein Disposal System

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

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

The UPS induces DEGRADATION OF DAMAGED OR UNNEEDED PROTEINS



Protein
Misfolded, damaged, or unneeded

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

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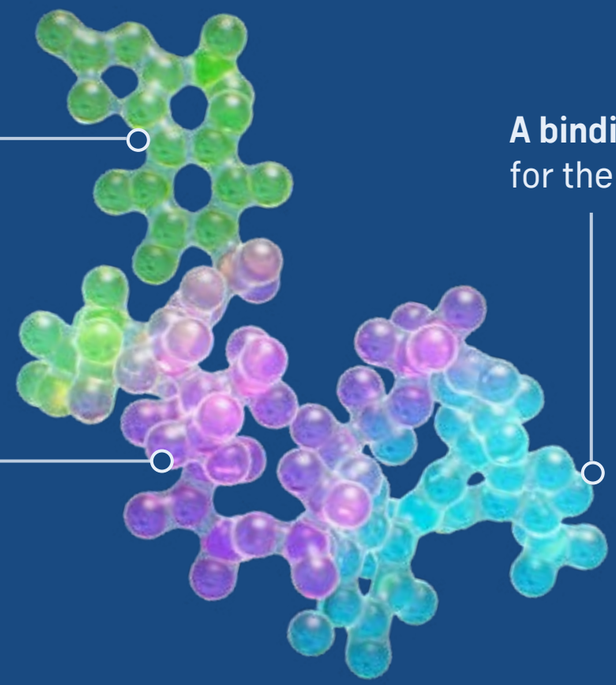
Unique Molecular Design

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

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Targeted Protein Degradation

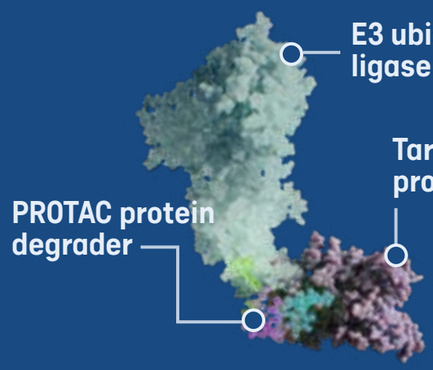
PROTAC protein degraders are designed to directly induce the ubiquitin-proteasome system (UPS) to eliminate the target protein.

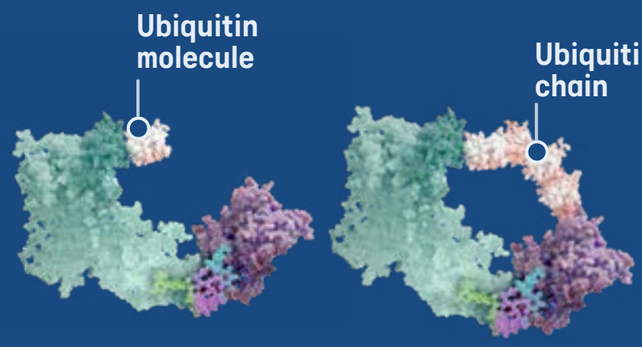
Recruitment of the UPS

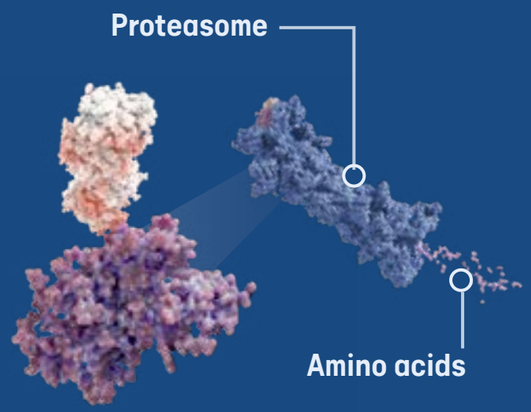
1 Ternary Complex
The unique design results in the formation of a ternary complex consisting of the PROTAC molecule, the target protein and the E3 ligase

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 ubiquinated target protein will be directed to the proteasome where it is subsequently degraded







See how this process repeats

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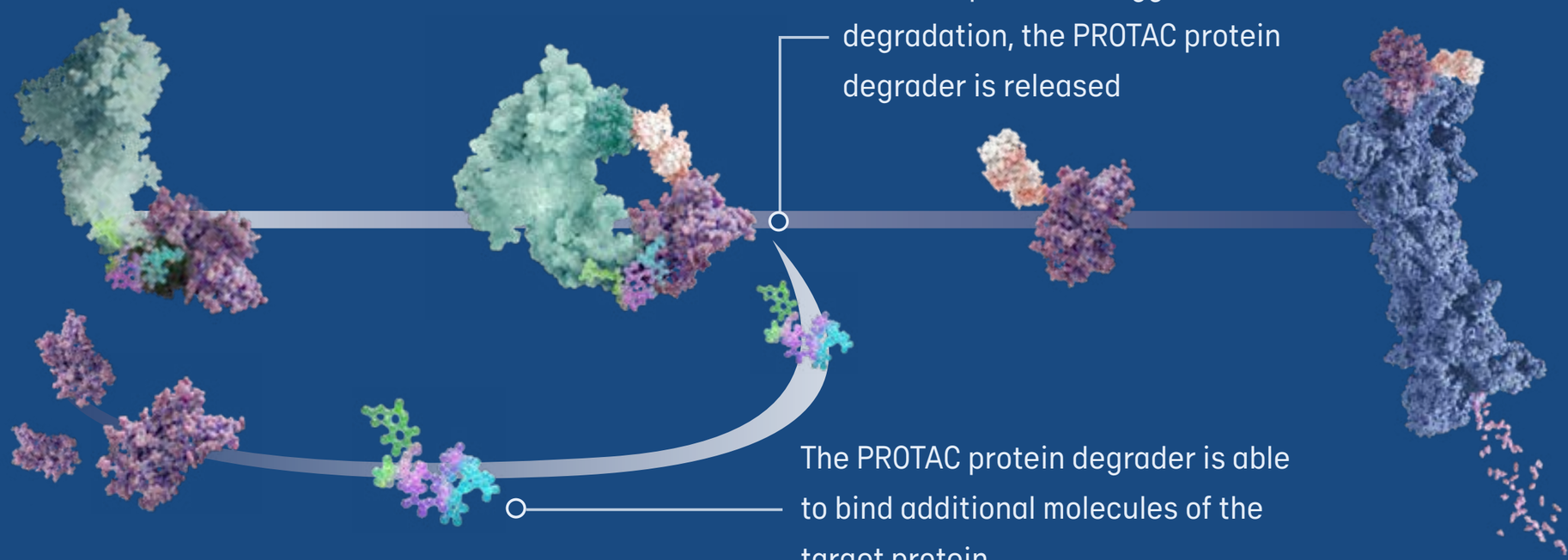
Repeat Degradation

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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Target protein

PROTAC
Protein D

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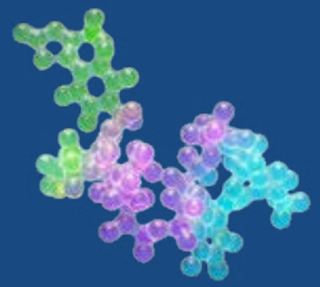
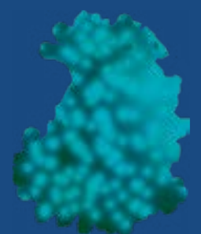
The ubiquinated target protein is recognized and **degraded** by the proteasome



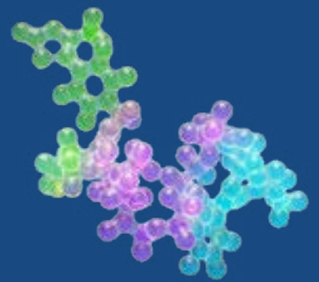
The PROTAC Protein Degrader Difference

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 Degraders have many potential applications beyond traditional small molecule inhibitors.



Traditional Small Molecule Inhibitors



PROTAC Protein Degraders

Typically inhibit enzymatic functions	Designed to 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

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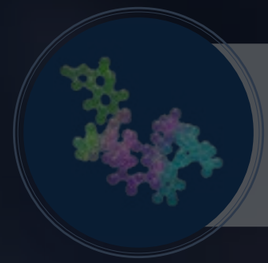

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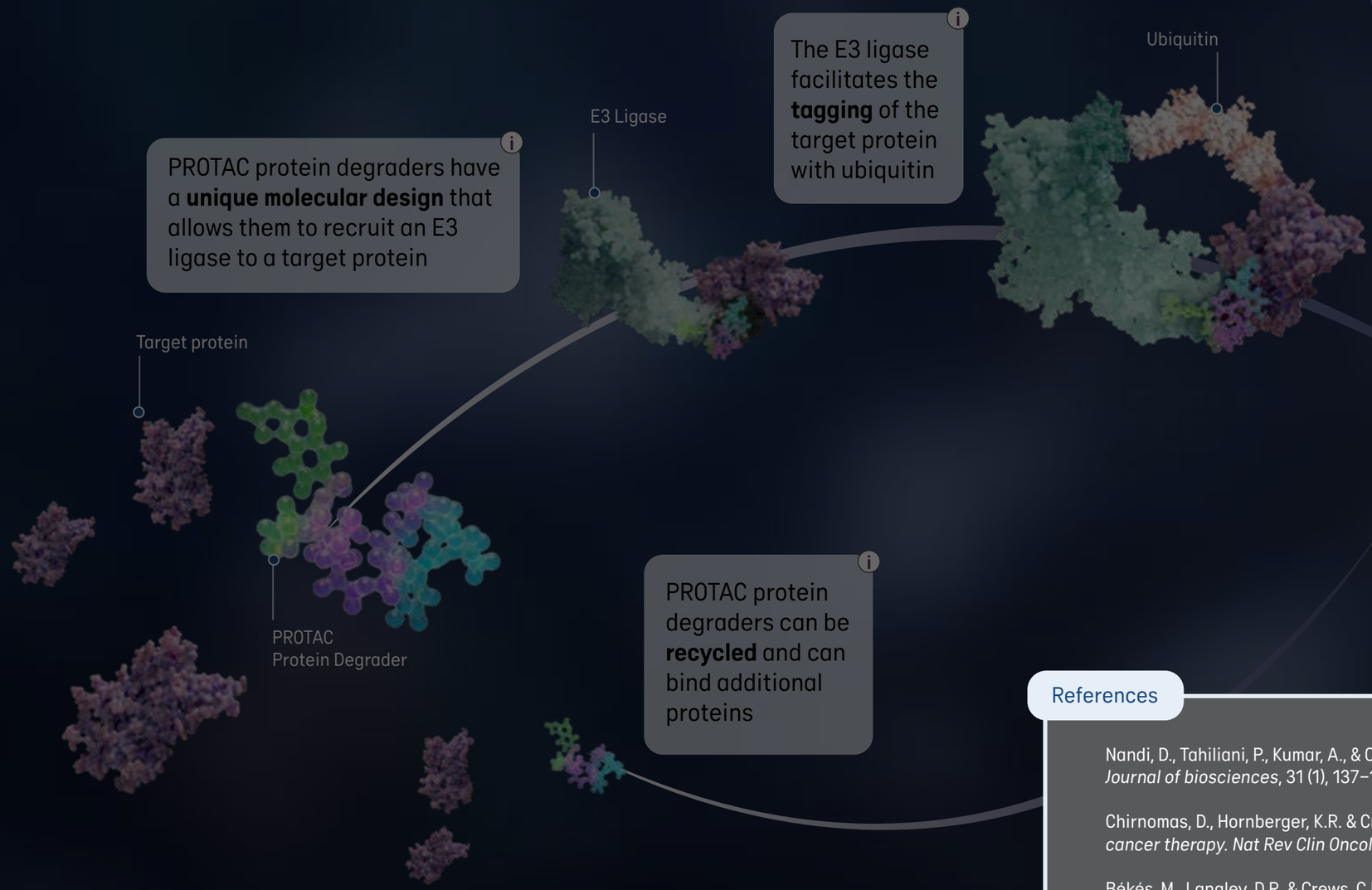

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References

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