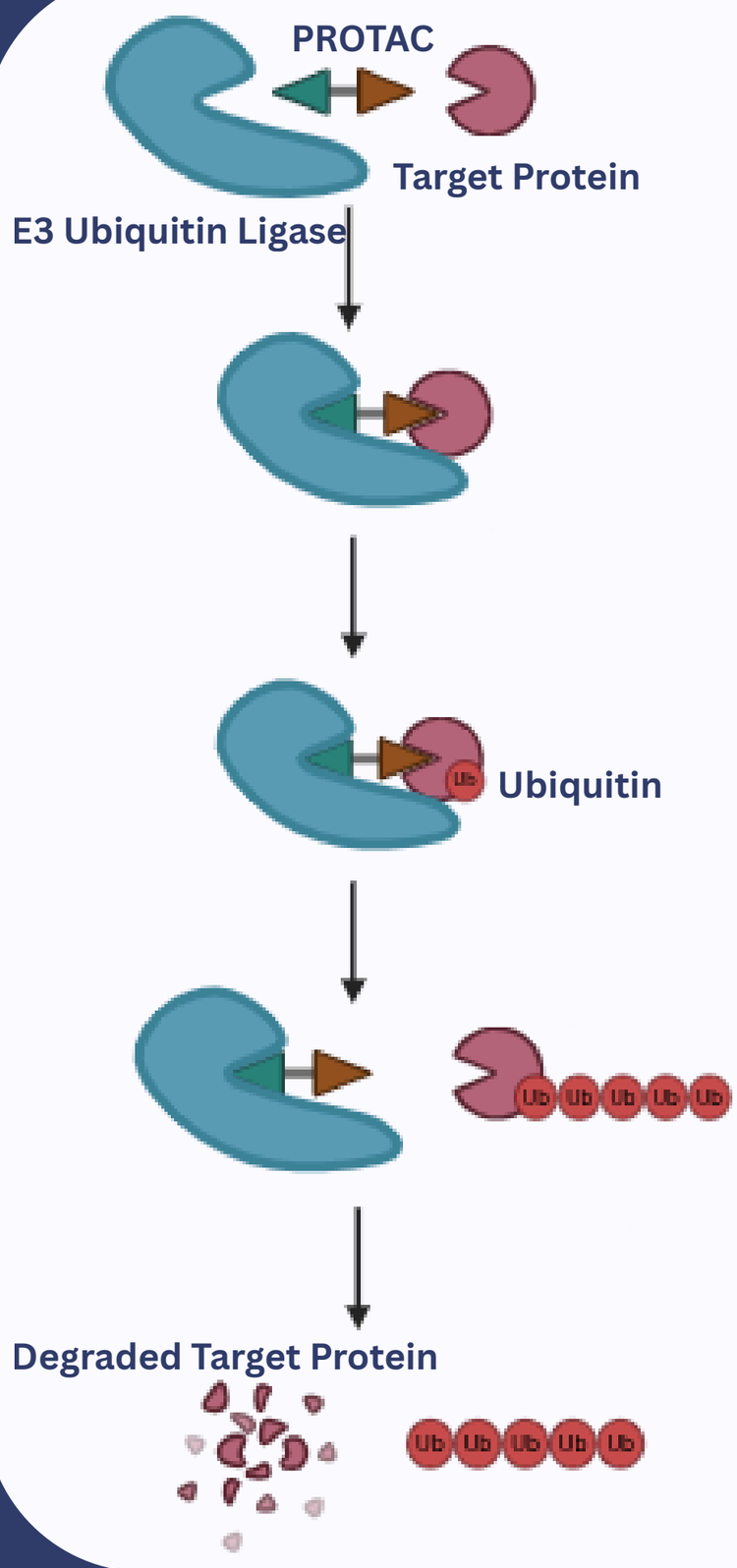
Potential of PROTACs in Selective Cancer Therapy

Cancer cells are able to proliferate uncontrollably, invade nearby tissue and spread to other parts of the body. With 346,217 new cases of cancer and 138,570 deaths in England in 2022 and no current cure, we need a breakthrough to improve treatment outcomes. PROTACs could be what we need.

Proteolysis targeting Chimeras (**PROTACs**) are engineered molecules which target **specific proteins** and lead to their **degradation**. PROTACs promise selective targeted therapy to improve cancer patient **survival** and **quality** of life.



- **PROTACs hijack the cell's protein degradation system.**
- **The PROTAC selectively binds to both the Target Protein and E3 Ubiquitin Ligase so they are in close enough proximity for E3 Ubiquitin Ligase to add Ubiquitin to the Target Protein.**
- **This tells the cell that the protein must be degraded.**

What are PROTACs, E3 Ubiquitin Ligase and Ubiquitin?

PROTACs are molecular handcuffs which capture and hold the target protein and E3 Ubiquitin Ligase together.

E3 Ubiquitin Ligase is the quality control inspector which identifies and tags faulty proteins for degradation.

Ubiquitin is a tag which signals to the cell that a protein must be degraded.

This means that PROTACs can be used to **degrade proteins** which increase cancer cell **proliferation**.

ARV-471 is a PROTAC which targets estrogen recepors (**ER**) in ER+ metastatic breast cancer. Degradation of ER means that there is less DNA **replication** therefore decreased cancer cell **proliferation**. ARV-471 has reached **Stage III** of clinical studies and has shown impressive results in the pre-clinical studies with up to **97%** ER degradation in tumour cells leading to induced tumour **shrinkage** and increased **anti-tumour activity.**

PROTACs have many advantages over chemotherapy:

- **PROTACs allow lower doses than small-molecule drugs. Therefore fewer side effects.**
- **PROTACs degrade "undruggable" targets, such as DNA-binding proteins, which are difficult to inhibit with traditional drugs.**

However, PROTACs also have limitations:

- **PROTACs have a higher molecular weight therefore a lower cell permeability and solubility than small-molecule drugs. This limits their targeting capabilities.**
- **Some E3 Ubiquitin Ligases have low specificity causing the PROTACs to have off target effects.**

There may be solutions to these limitations:

- **To increase cell permeability, long and flexible linkers could be used.**
- **To decrease off target effects, identifying specific E3 Ubiquitin Ligases could be critical.**

Further Reading:

What Is Cancer? - NCI [Internet]. 2007 [cited 2025 Aug 16]. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer

Li X, Pu W, Zheng Q, Ai M, Chen S, Peng Y. Proteolysis-targeting chimeras (PROTACs) in cancer therapy. Molecular Cancer. 2022 Apr 11;21(1):99.

Wang X, Qin ZL, Li N, Jia MQ, Liu QG, Bai YR, et al. Annual review of PROTAC degraders as anticancer agents in 2022. European Journal of Medicinal Chemistry. 2024 Mar 5;267:116166.

Arvinas and Pfizer's Vepdegestrant (ARV-471) Receives FDA Fast Track Designation for the Treatment of Patients with ER+/HER2- Metastatic Breast Cancer | Pfizer [Internet]. [cited 2025 Aug 16]. Available from: https://www.pfizer.com/news/announcements/arvinas-and-pfizers-vepdegestrant-arv-471-receives-fda-fast-track-designation

PROTACs offer a promising new approach to cancer therapy through selective targeting of specific proteins for degradation, leading to decreased cancer cell **proliferation**. In pre-clinical trials PROTACs have shown encouraging results with ARV-471 reaching an advanced stage of clinical trial. The ability of PROTACs to degrade "**undruggable**" proteins combined with fewer **side effects** makes them an attractive alternative to chemotherapy. As cancer remains a leading cause of death worldwide and PROTACs continue to advance through clinical trials, they provide hope and promise of **better** patient survival and quality of life.