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PROTACS: Targeted Therapies for Precision Medicine

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PROTACs, or Proteolysis-Targeting Chimeras, are a class of compounds used in pharmacology that have gained significant attention in recent years. PROTACs are designed to induce the targeted degradation of specific proteins within cells. This is achieved by recruiting a cell's own protein degradation machinery to design the protein of interest for destruction. The PROTAC molecule acts as a bridge, bringing the designed protein into proximity with a ubiquitin ligase, which tags the protein with ubiquitin, leading to its breakdown by the proteasome (1).

Mechanism of Action

Ternary Complex Formation: PROTACs typically consist of three components - a ligand for the target protein, a ligand for a ubiquitin ligase, and a linker connecting them. When a PROTAC binds to the designed protein, it also binds to the E3 ligase, forming a ternary complex (2). Ubiquitination and Degradation: This ternary complex recruit ubiquitin molecules to designed protein, marking it for breakdown by the proteasome.

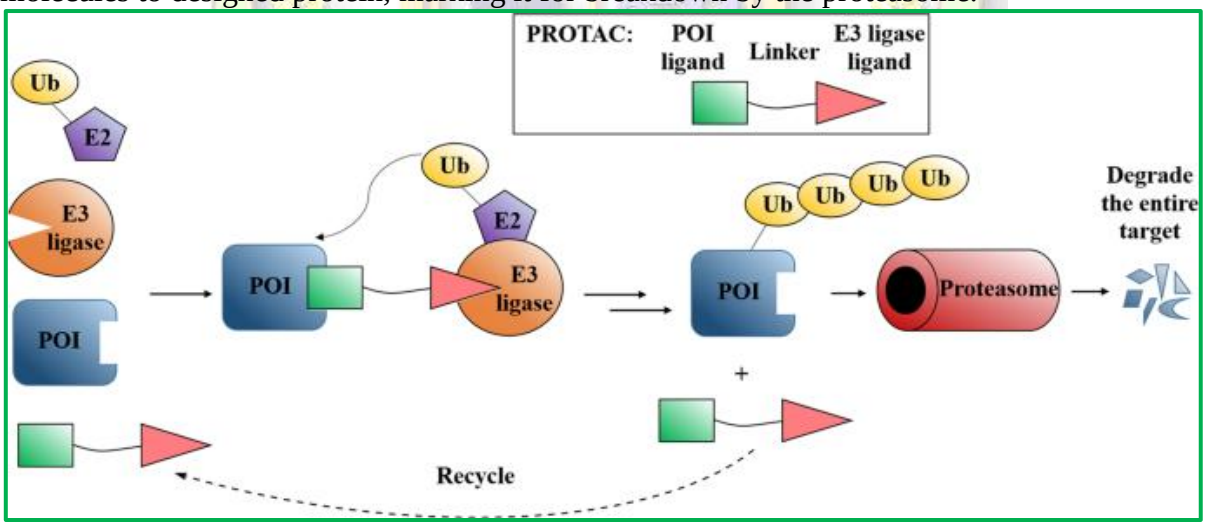

Fig 1: Schematic representation of PROTACs Mechanism of Action (2)

Advantages of PROTACs (3):

PROTACs (Proteolysis-Targeting Chimeras) offer several advantages in drug development and therapeutic applications. Here are some general advantages of PROTAC technology:

High Selectivity: PROTACs can be designed with high specificity for the target protein, allowing for precise targeting of disease-associated proteins while minimizing off-target effects.

Unique Mode of Action: PROTACs induce targeted protein degradation rather than inhibition. This can be advantageous in situations where inhibition alone may not be sufficient to achieve the desired therapeutic effect.

Potential for "Undruggable" Targets: PROTACs can target proteins that have been traditionally considered challenging to inhibit using small molecules, including proteins lacking well-defined binding pockets.

Reduction of Drug Resistance: By inducing breakdown of the designed protein, PROTACs may help overcome mechanisms of drug resistance that can arise from prolonged inhibition.

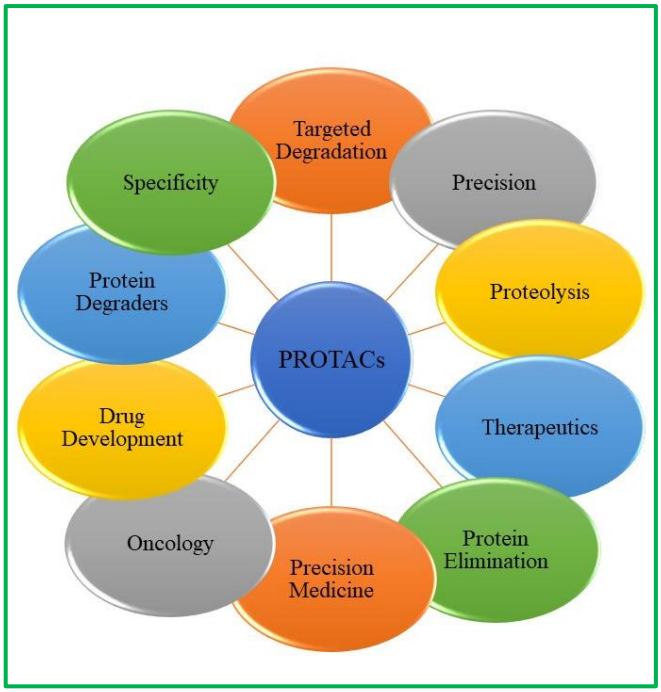

Fig 2: Schematic representation of advantages of PROTACs

Extended Duration of Action: The degradation of target proteins by PROTACs may result in a more prolonged therapeutic effect compared to reversible inhibition.

Applicability to Diverse Targets: PROTACs are a versatile technology that can be applied to a wide range of designed proteins, making them suitable for various disease indications.

Combination Therapy Potential: PROTACs may be used in conjunction with other drugs or therapeutic modalities to enhance treatment efficacy through synergistic effects.

Reduced Side Effects: The targeted nature of PROTACs may lead to reduced side effects in contrast to traditional small-molecule inhibitors that can affect multiple proteins.

Potential for Oral Administration: Some PROTACs are designed to be orally bioavailable, providing a convenient and patient-friendly route of administration.

Therapeutic Opportunities in Multiple Disease Areas: PROTACs have shown promise in various disease areas, including cancer, neurodegenerative diseases, and autoimmune disorders, expanding their potential therapeutic applications.

Adaptability to Drug Design: PROTACs can be rationally designed and optimized based on the particular properties of the designed protein and E3 ligase, allowing for flexibility in drug development.

Precision: PROTACs offer a high degree of specificity, targeting a particular protein for degradation.

Applications in Drug Development

1. **Cancer Therapy:** PROTACs have shown promise in cancer therapy by targeting specific proteins implicated in cancer cell survival and proliferation.
2. **Neurodegenerative Diseases:** There is ongoing research into using PROTACs for neurodegenerative diseases by targeting specific proteins involved in disease progression.

Challenges

1. **Design Complexity:** Designing effective PROTACs involves optimizing the linker length, ligand affinities, and other factors for both the designed protein and the E3 ligase.
2. **Delivery:** Efficient delivery of PROTACs to the target cells poses challenges, especially if they need to reach specific tissues or organs.

PROTACs in Research and Development

Drug Development Pipeline: Several pharmaceutical companies and research institutions are actively working on developing PROTAC-based therapies, and several compounds are in various stages of preclinical and clinical advancement. The PROTAC field was an active area of research, and several PROTAC drugs were in various stages of preclinical and clinical advancement. However, the specific details and statuses of these compounds can change rapidly. Here are a few PROTAC drugs that were in development or undergoing clinical trials mentioned in table 1 (4, 5, 6, 7, 8, & 9).

Drug	Target	Development Stage	Indication
ARV-110	AR	Early-phase clinical trials	Metastatic castration-resistant prostate cancer
ARV-471	ER	Investigational drug	ER-positive / HER2-negative breast cancer
ARV-825	AR and BRD4	Preclinical development	Prostate cancer
GDC-0810	ER	Investigational drug	ER-positive breast cancer
DT2216	BCL-XL	Preclinical development	Various cancers
CTA101	EGFR	Preclinical development	Cancer therapy

Note: Androgen Receptor-AR, Estrogen Receptor-ER, Bromodomain-containing protein 4 - BRD4, B-cell lymphoma-extra-large-BCL-XL and Epidermal Growth Factor Receptor-EGFR

Conclusion

In conclusion, PROTACs represent a groundbreaking approach in precision medicine, offering high selectivity, a unique mode of action, and applicability to diverse disease areas. The advantages of PROTACs, including their potential for targeting "undruggable" proteins and reducing drug resistance, make them a promising avenue for therapeutic development. While challenges such as design complexity and efficient delivery exist, ongoing research and development efforts are actively addressing these issues. The current pipeline of PROTAC drugs in various stages of development underscores their potential across multiple disease indications, with notable progress observed in cancer therapy and neurodegenerative diseases. As PROTACs continue to advance, they hold the promise of transforming drug development and enhancing therapeutic precision.

References

1. Hu, Z., & Crews, C. M. (2022). Recent developments in PROTAC-mediated protein degradation: from bench to clinic. *ChemBioChem*, *23*(2), e202100270.
2. Sun, X., Gao, H., Yang, Y., He, M., Wu, Y., Song, Y., ... & Rao, Y. (2019). PROTACs: great opportunities for academia and industry. *Signal transduction and targeted therapy*, *4*(1), 64.
3. Li, K., & Crews, C. M. (2022). PROTACs: past, present and future. *Chemical Society Reviews*, *51*(12), 5214-5236.
4. Neklesa, T., Snyder, L. B., Willard, R. R., Vitale, N., Pizzano, J., Gordon, D. A., ... & Taylor, I. (2019). ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. *J. Clin. Oncol*, *37*(259), 10-1200.
5. Snyder, L. B., Flanagan, J. J., Qian, Y., Gough, S. M., Andreoli, M., Bookbinder, M., ... & Chandler, J. (2021). The discovery of ARV-471, an orally bioavailable estrogen

receptor degrading PROTAC for the treatment of patients with breast cancer. *Cancer Res*, *81*(13), 44.

6. Wu, S., Jiang, Y., Hong, Y., Chu, X., Zhang, Z., Tao, Y., ... & Hu, S. (2021). BRD4 PROTAC degrader ARV-825 inhibits T-cell acute lymphoblastic leukemia by targeting'Undruggable'Myc-pathway genes. *Cancer Cell International*, *21*(1), 1-16.
7. Rej, R. K., Thomas, J. E., Acharyya, R. K., Rae, J. M., & Wang, S. (2023). Targeting the estrogen receptor for the treatment of breast cancer: recent advances and challenges. *Journal of Medicinal Chemistry*, *66*(13), 8339-8381.
8. Champion, O., Soler, A., Maïga, S., Bellanger, C., Pellat-Deceunynck, C., Talbot, A., ... & Gomez-Bougie, P. (2023). BCLXL PROTAC degrader DT2216 targets secondary plasma cell leukemia addicted to BCLXL for survival. *Frontiers in Oncology*, *13*.
9. Zhang, H., Zhao, H. Y., Xi, X. X., Liu, Y. J., Xin, M., Mao, S., ... & Zhang, S. Q. (2020). Discovery of potent epidermal growth factor receptor (EGFR) degraders by proteolysis targeting chimera (PROTAC). *European Journal of Medicinal Chemistry*, *189*, 112061.