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Supplementary information

The targeted protein degradation landscape

In the format provided by the authors and unedited

Database assembly and analysis

We assembled a comprehensive database of 256 targeted protein degraders (TPD) across all research, preclinical, clinical development, and marketed assets as of September 2024.

Core source. We compiled our initial set of assets using the EvaluatePharma database. To identify relevant assets, we filtered the database based on keywords ("degrader", "PROteolysis Targeting Chimera", "PROTAC", "BiDAC", "immunomodulatory drug", "IMiD", "Cereblon E3 ligase modulatory drugs", "CELMoD", "SERD", "molecular glue", variations) in the "Mechanism of Action" or the "Pharmaceutical Class" columns in the overall EvaluatePharma R&D pipeline database.

Validation. We manually cross-checked the resulting database against company websites to classify the mechanism as TPD, resulting in the removal of ~20 assets misclassified as TPDs (such as inhibitors, agonists, suppressors). To verify that our list was up to date, we scanned recent press releases, conference presentations, academic publications, and company websites using the same TPD keywords. This scan resulted in the addition of two assets that had been recently progressed into the clinic, and the removal of six assets that had been recently discontinued. Given the capture biases of EvaluatePharma, we anticipate lower coverage of research, preclinical, and ex-US/EU assets.

Technology. For assets classified as TPDs, we classified them based on technology, into current-generation, next-generation, and not specified. Current technologies are: molecular glue (inclusive of IMiDs and CELMoDs); heterobifunctional degrader (inclusive of small-molecule heterobifunctional degraders that directly recruit a ubiquitously expressed E3 ligase, e.g. PROTACs); selective estrogen receptor degrader (SERD). Next-generation technologies in the pipeline are: degrader–antibody conjugate (DAC); molecular degrader of extracellular protein (MoDE); chaperone-mediated (CHAMP); autophagy (AUTAC). Note that estrogen receptor degraders are classified as SERDs versus heterobifunctional degraders based on molecular structure and mechanism; for example, elacestrant is classified as a SERD, while vepdegestrant is classified as a heterobifunctional degrader. Also note that three heterobifunctional "autophagy stimulants" with undisclosed structures are classified as AUTACs given comparison between program initiation and the state of autophagy research, but may be similar autophagy technologies (such as ATTEC).

Stage of development. "Approved" assets are currently approved. "Clinic" assets are currently in phase I-III clinical trials as established using ClinicalTrials.gov and/or the company website. "Research" assets are currently in active research or preclinical development, confirmed using press releases and/or the company website.

Therapeutic area. For marketed assets, we manually the confirmed therapeutic area using approval press releases and drug inserts. For clinical assets, we manually confirmed therapeutic area using ClinicalTrials.gov and/or the company website; if several clinical trials for an asset existed, the most advanced trial was used to determine therapeutic area. For research and preclinical assets, we extracted the therapeutic area from the EvaluatePharma database. Therapeutic areas were consolidated into the three categories with the highest number of assets (cancer, neurology and immunology), then "other," inclusive of urinary tract, infections, respiratory, skin, diabetes, gastrointestinal, musculoskeletal, hepatic, blood, cardiovascular, urinary tract, and miscellaneous (each with 1–5 assets).

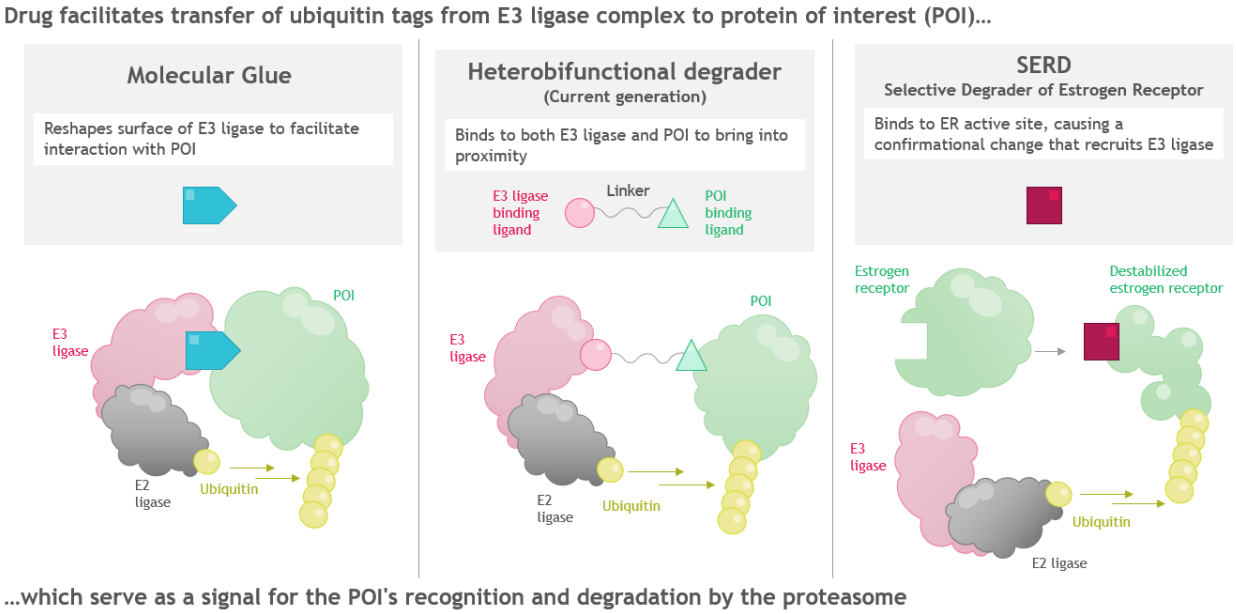
Target. For marketed assets, we manually confirmed the target protein using approval press releases and drug inserts. For clinical assets, we manually confirmed the target protein using ClinicalTrials.gov and/or the company website. For research and preclinical assets, target proteins were determined based on manual inspection of key words in the "Mechanism of Action" and "Pharmaceutical Class" fields, such as SMARCA2 degrader, alpha-synuclein (SNCA) degrader, supplemented with company websites, press releases, and Citeline.

Druggability of target. Classically druggable targets are well-studied, with existing traditional drugs (such as small molecules and monoclonal antibodies), and are typically an enzyme or receptor with a druggable pocket (such as the estrogen receptor, androgen receptor, BTK). Classically undruggable targets have no approved, robust small-molecule/monoclonal antibody drug that targets them. The vast majority of these are targets with no approved traditional drugs, but this category also includes a handful of difficult-to-drug targets that have approved traditional drugs with limited scope; for example, CDK4 cannot be targeted selectively by existing inhibitors jointly targeting CDK4 and CDK6 and only G12-mutant-KRAS can be targeted by approved inhibitors. Undruggable targets generally are proteins with non-enzymatic activity (such as MYC, STAT3, Ikaros), lacking druggable pockets (such as Tau, KRAS, GSPT1, SMARCA2), involved in complex systems of protein–protein interactions (such as NLRP3, IKZF2, ARID1B), or sharing domains with other proteins that complicate selectivity (such as Wee1, SCNA, BRD4/9, CDK2/4/9/12). For assets that degrade multiple targets (such as many molecular glues), the target was considered classically undruggable if any of the targets are classically undruggable.

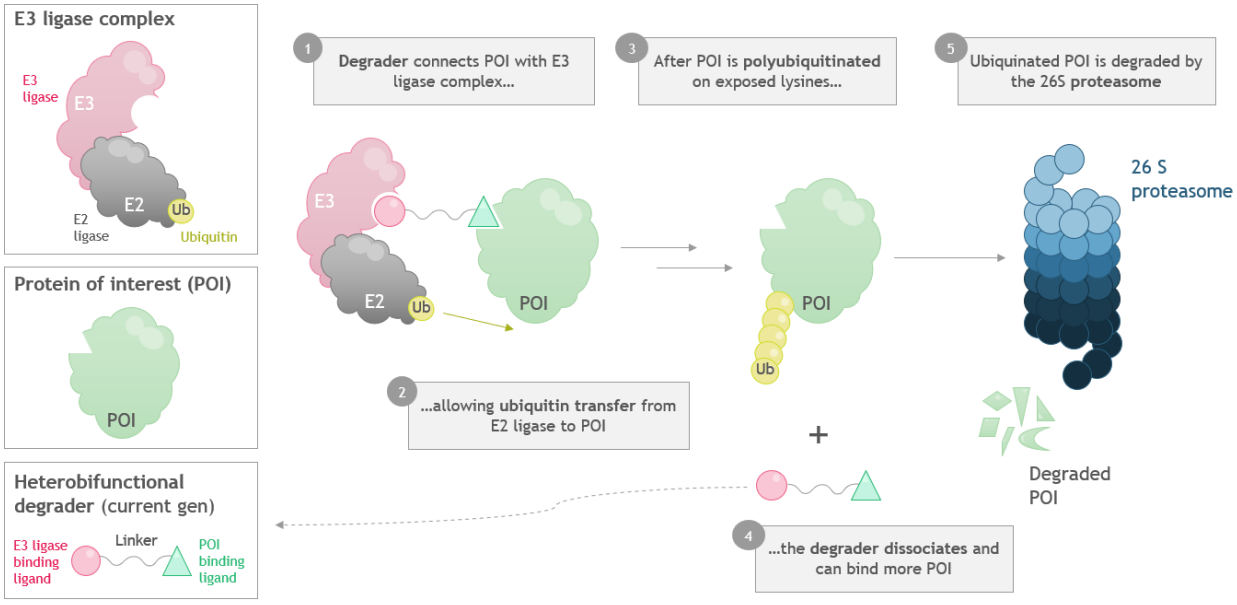
***Assessment of next-generation technology*.** We evaluated a subset of next-generation TPD technologies across academic publications, pharmaceutical/biotech research programs, and clinical trials. We selected a representative set of possible developments across innovations in pathway, delivery, ligands, or activation, with a bias towards assets that were more developed (that is, more citations in the literature, or more activity in industry). Evaluation of the profile of different technologies is based on review of the literature (with more weight placed on advanced studies such as in vivo studies when available) and, when no clear data was available, the general properties of the class (for example, small molecules, peptides and antibodies).

	Targeted protein degradation*	**Small-molecule inhibitor**	**Monoclonal antibody**	**RNA interference**
Intracellular targets	+	+		+
Extracellular targets		+	+	+
Active site independence	+			+
Removal of direct and ancillary protein functions	+			+
Selectivity	+		+	+
Oral bioavailability	+	+		
Catalytic mechanism	+			+
Lasting effect after drug removal	+			+
Small-molecule synthesis	+	+		

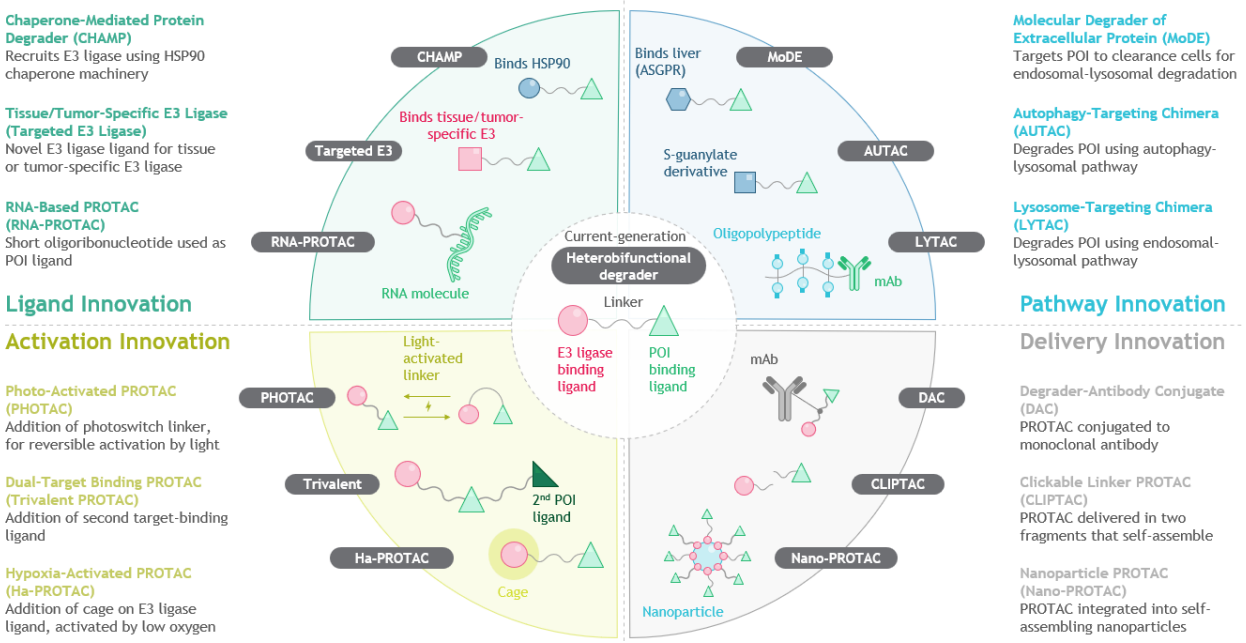
Supplementary Fig. 1 | **Comparison of targeted protein degradation to other modalities.** High-level comparison of relative strengths (indicated by a +) of current* targeted protein degradation technologies (molecular glues, heterobifunctional degraders, selective estrogen receptor degraders) to traditional modalities (small-molecule inhibitor, monoclonal antibody) and similar new modalities (RNA interference).



Supplementary Fig. 2 | **Summary mechanism of current TPD technologies.** Schematic representation of transfer of ubiquitin tags to protein of interest (POI) by molecular glue, heterobifunctional degrader, and selective estrogen receptor degrader (SERD). Each drug recruits an E3 ligase complex to the POI, thereby facilitating the transfer of ubiquitin from E2 ligase to exposed lysines on the POI.



Supplementary Fig. 3 | **Detailed mechanism of heterobifunctional degrader-triggered degradation.** Schematic representation of how a heterobifunctional degrader results in the polyubiquitination of a protein of interest (POI). After polyubiquitination, the degrader dissociates and is free to bind more POIs, and the ubiquitinated POI is degraded by the proteasome.



Supplementary Fig. 4 | **Description of next-generation targeted protein degradation technologies.** Brief description and visual representation of next-gen targeted protein degradation technologies, organized by type of innovation (ligand, pathway, delivery, and activation).

Key references

Alabi, S. B., & Crews, C. M. (2021). Major advances in targeted protein degradation: PROTACs, LYTACs, and MADTACs. *The Journal of Biological Chemistry*, *296*, 100647. https://doi.org/10.1016/j.jbc.2021.100647

Arvinas and Pfizer Announce Updated Clinical Data from Phase 1b Trial of Vepdegestrant in Combination with Palbociclib. (2024, May 16). Arvinas. https://ir.arvinas.com/news-releases/news-release-details/arvinas-and-pfizer-announce-updated-clinical-data-phase-1b-trial

ARV-766 shows promising efficacy and tolerability in mCRPC. (2024, June 4). Urology Times. https://www.urologytimes.com/view/arv-766-shows-promising-efficacy-and-tolerability-in-mcrpc

Békés, M., Langley, D. R., & Crews, C. M. (2022). PROTAC targeted protein degraders: The past is prologue. *Nature Reviews Drug Discovery*, *21*(3), 181–200. https://doi.org/10.1038/s41573-021-00371-6

Chirnomas, D., Hornberger, K. R., & Crews, C. M. (2023). Protein degraders enter the clinic—A new approach to cancer therapy. *Nature Reviews. Clinical Oncology*, *20*(4), 265–278. https://doi.org/10.1038/s41571-023-00736-3

Cristofanilli, M., Turner, N. C., Bondarenko, I., Ro, J., Im, S. A., Masuda, N., Colleoni, M., DeMichele, A., Loi, S., Verma, S., Iwata, H., Harbeck, N., Zhang, K., Theall, K. P., Jiang, Y., Bartlett, C. H., Koehler, M., & Slamon, D. (2016). Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): Final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *The Lancet Oncology*, *17*(4), 425–439. https://doi.org/10.1016/S1470-2045(15)00613-0

C4 Therapeutics presents new preclinical data on CFT1946. (2024, September 10). C4 Therapeutics. https://ir.c4therapeutics.com/news-releases/news-release-details/c4-therapeutics-presents-new-preclinical-data-cft1946

Delivering on a promise: The present and future of targeted protein degradation. (2021, March 4). GEN - Genetic Engineering and Biotechnology News. https://www.genengnews.com/topics/drug-discovery/delivering-on-a-promise-the-present-and-future-of-targeted-protein-degradation/

Ding, Y., Xing, D., Fei, Y., & Lu, B. (2022). Emerging degrader technologies engaging lysosomal pathways. *Chemical Society Reviews*, *51*(21), 8832–8876. https://doi.org/10.1039/d2cs00624c

Dong, G., Ding, Y., He, S., & Sheng, C. (2021). Molecular glues for targeted protein degradation: From serendipity to rational discovery. *Journal of Medicinal Chemistry*, *64*(15), 10606–10620. https://doi.org/10.1021/acs.jmedchem.1c00895

End of the line for Sanofi's SERD amcenestrant as it fails first-line trial. (2022, August 17). Pharmaphorum. https://pharmaphorum.com/news/end-of-the-line-for-sanofis-serd-amcenestrant-as-it-fails-first-line-trial

Fang, Y., Wang, S., Han, S., Zhao, Y., Cunjing, Y., Liu, H., & Li, N. (2023). Targeted protein degrader development for cancer: advances, challenges, and opportunities. *Trends in Pharmacological Sciences, 44*(5), P303-317. https://doi.org/10.1016/j.tips.2023.03.003

Feuerstein, A. (2024, May 29). Biohaven protein-degrader drug falls short of investor expectations in early-study test. *STAT*. https://www.statnews.com/2024/05/29/biohaven-protein-degrader-drug-data/

Gao, J., Hou, B., Zhu, Q., Yang, L., Jiang, X., Zou, Z., Li, X., Xu, T., Zheng, M., Chen, Y.-H., Xu, Z., Xu, H., & Yu, H. (2022). Engineered bioorthogonal POLY-PROTAC nanoparticles for tumour-specific protein degradation and precise cancer therapy. *Nature Communications*, *13*, 4318. https://doi.org/10.1038/s41467-022-32050-4

Ghidini, A., Cléry, A., Halloy, F., Allain, F. H. T., & Hall, J. (2021). RNA-PROTACs: Degraders of RNA-Binding Proteins. *Angewandte Chemie (International ed. in English)*, *60*(6), 3163–3169. https://doi.org/10.1002/anie.202012330

Gooding, S., Ansari-Pour, N., Towfic, F., Ortiz Estévez, M., Chamberlain, P. P., Tsai, K. T., Flynt, E., Hirst, M., Rozelle, D., Dhiman, P., Neri, P., Ramasamy, K., Bahlis, N., Vyas, P., & Thakurta, A. (2021). Multiple Cereblon genetic changes are associated with acquired resistance to lenalidomide or pomalidomide in multiple myeloma. *Blood*, *137*(2), 232–237. https://doi.org/10.1182/blood.2020007081

Han, X., & Sun, Y. (2022). Strategies for the discovery of oral PROTAC degraders aimed at cancer therapy. *Cell Reports Physical Science*, *3*(10), 101062. https://doi.org/10.1016/j.xcrp.2022.101062

He, Q., Zhao, X., Wu, D., Jia, S., Liu, C., Cheng, Z., Huang, F., Chen, Y., Lu, T., & Lu, S. (2023). Hydrophobic tag-based protein degradation: Development, opportunity and challenge. *European Journal of Medicinal Chemistry*, *260*, 115741. https://doi.org/10.1016/j.ejmech.2023.115741

Imaide, S., Riching, K. M., Makukhin, N., Vetma, V., Whitworth, C., Hughes, S. J., Trainor, N., Mahan, S. D., Murphy, N., Cowan, A. D., Chan, K. H., Craigon, C., Testa, A., Maniaci, C., Urh, M., Daniels, D. L., & Ciulli, A. (2021). Trivalent PROTACs enhance protein degradation via combined avidity and cooperativity. *Nature chemical biology*, *17*(11), 1157–1167. https://doi.org/10.1038/s41589-021-00878-4

Investors turn cold on Biohaven after protein degrader results. (2024, June 7). Synapse. https://synapse.patsnap.com/article/investors-turn-cold-on-biohaven-after-protein-degrader-results

Ishida, T., & Ciulli, A. (2021). E3 ligase ligands for protacs: How they were found and how to discover new ones. *SLAS Discovery: Advancing Life Sciences R & D*, *26*(4), 484–502. https://doi.org/10.1177/2472555220965528

Kruger, A. (2021, October 21). *The power of binding: Using trivalent protacs to enhance protein degradation*. Promega Connections. https://www.promegaconnections.com/the-power-of-binding-using-trivalent-protacs-to-enhance-protein-degradation/

Li, K., & Crews, C. M. (2022). PROTACs: Past, present and future. *Chemical Society Reviews*, *51*(12), 5214–5236. https://doi.org/10.1039/d2cs00193d

Lu, J., Qian, Y., Altieri, M., Dong, H., Wang, J., Raina, K., Hines, J., Winkler, J. D., Crew, A. P., Coleman, K., & Crews, C. M. (2015). Hijacking the E3 ubiquitin ligase Cereblon to efficiently target BRD4. *Chemistry & Biology*, *22*(6), 755–763. https://doi.org/10.1016/j.chembiol.2015.05.009

Mode™ | molecular degraders of extracellular proteins. (n.d.). *Biohaven, Ltd.* Retrieved September 29, 2024, from https://www.biohaven.com/pipeline/igg-degrader/

Molecular glues clinical trial pipeline appears robust with 10+ key pharma companies actively working in the therapeutics segment (2024). PR Newswire. https://www.prnewswire.com/news-releases/molecular-glues-clinical-trial-pipeline-appears-robust-with-10-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302194515.html

Nalawansha, D. A., & Crews, C. M. (2020). Protacs: An emerging therapeutic modality in precision medicine. *Cell Chemical Biology*, *27*(8), 998–1014. https://doi.org/10.1016/j.chembiol.2020.07.020

Oleinikovas, V., Gainza, P., Ryckmans, T., Fasching, B., & Thomä, N. H. (2024). From thalidomide to rational molecular glue design for targeted protein degradation. *Annual Review of Pharmacology and Toxicology*, *64*(1), 291–312. https://doi.org/10.1146/annurev-pharmtox-022123-104147

Orum therapeutics presents positive preclinical data of orm-6151, a first-in-class, cd33-gspt1 dual-precision targeted protein degrader for aml, at ash 2022. (2022, December 10). Orum Therapeutics. https://www.orumrx.com/news/blog-post-title-one-wpann

Pathmanathan, S., Grozavu, I., Lyakisheva, A., & Stagljar, I. (2022). Drugging the undruggable proteins in cancer: A systems biology approach. *Current Opinion in Chemical Biology*, *66*, 102079. https://doi.org/10.1016/j.cbpa.2021.07.004

Pettersson, M., & Crews, C. M. (2019). Proteolysis targeting chimeras (PROTACs)—Past, present and future. *Drug Discovery Today: Technologies*, *31*, 15–27. https://doi.org/10.1016/j.ddtec.2019.01.002

Reynders, M., Matsuura, B. S., Bérouti, M., Simoneschi, D., Marzio, A., Pagano, M., & Trauner, D. (2020). PHOTACs enable optical control of protein degradation. *Science Advances*, *6*(8), eaay5064. https://doi.org/10.1126/sciadv.aay5064

Potential Arvinas PROTAC® AR degraders reinforced 11.1 months. (2024, September 10). Arvinas. https://ir.arvinas.com/news-releases/news-release-details/potential-arvinas-protacr-ar-degraders-reinforced-111-months

Qi, S.-M., Dong, J., Xu, Z.-Y., Cheng, X.-D., Zhang, W.-D., & Qin, J.-J. (2021). Protac: An effective targeted protein degradation strategy for cancer therapy. *Frontiers in Pharmacology*, *12*, 692574. https://doi.org/10.3389/fphar.2021.692574

Sasso, J. M., Tenchov, R., Wang, D., Johnson, L. S., Wang, X., & Zhou, Q. A. (2023). Molecular glues: The adhesive connecting targeted protein degradation to the clinic. *Biochemistry*, *62*(3), 601–623. https://doi.org/10.1021/acs.biochem.2c00245

Sobhani, N., Neeli, P. K., D'Angelo, A., Pittacolo, M., Sirico, M., Galli, I. C., Roviello, G., & Nesi, G. (2021). Ar-V7 in metastatic prostate cancer: A strategy beyond redemption. *International Journal of Molecular Sciences*, *22*(11), 5515. https://doi.org/10.3390/ijms22115515

Sun, X., Gao, H., Yang, Y., He, M., Wu, Y., Song, Y., Tong, Y., & Rao, Y. (2019). PROTACs: Great opportunities for academia and industry. *Signal Transduction and Targeted Therapy*, *4*(1), 1–33. https://doi.org/10.1038/s41392-019-0101-6

Wang, Y., & Tang, S.-C. (2022). The race to develop oral SERDs and other novel estrogen receptor inhibitors: Recent clinical trial results and impact on treatment options. *Cancer and Metastasis Reviews*, *41*(4), 975–990. https://doi.org/10.1007/s10555-022-10066-y

Xie, X., Yu, T., Li, X., Zhang, N., Foster, L. J., Peng, C., Huang, W., & He, G. (2023). Recent advances in targeting the "undruggable" proteins: From drug discovery to clinical trials. *Signal Transduction and Targeted Therapy*, *8*(1), 1–71. https://doi.org/10.1038/s41392-023-01589-z

Yao, T., Xiao, H., Wang, H., & Xu, X. (2022). Recent advances in protacs for drug targeted protein research. *International Journal of Molecular Sciences*, *23*(18), 10328. https://doi.org/10.3390/ijms231810328

Zhao, L., Zhao, J., Zhong, K., Tong, A., & Jia, D. (2022). Targeted protein degradation: Mechanisms, strategies and application. *Signal Transduction and Targeted Therapy*, *7*(1), 1–13. https://doi.org/10.1038/s41392-022-00966-4

Zhong, J., Zhao, R., Wang, Y., Su, Y., & Lan, X. (2024). Nano-PROTACs: State of the art and perspectives. *Nanoscale*, *16*(9), 4378–4391. https://doi.org/10.1039/D3NR06059D

Zhou, Q.-Q., Xiao, H.-T., Yang, F., Wang, Y.-D., Li, P., & Zheng, Z.-G. (2023). Advancing targeted protein degradation for metabolic diseases therapy. *Pharmacological Research*, *188*, 106627. https://doi.org/10.1016/j.phrs.2022.106627