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Recent Developments in Drug Discovery: From Artificial Intelligence to Targeted Protein Degradation

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Abstract: Artificial intelligence (AI) and targeted protein degradation (TPD) are changing drug discovery by introducing new methods for identifying targets and therapies. AI-powered methods like graph neural networks, deep learning,and generative models, are used throughout the drug development process. This includes selecting targets in silico, screening virtually, optimizing leads, and assessing preclinical safety. At the same time, TPD techniques, such as molecular glues and proteolysis-targeting chimeras (PROTACs), and LYTACs, let researchers selectively remove disease proteins by using cellular degradation systems.

This review summarizes recent advancements from 2019 to 2025 in both fields. We explore AI platforms and case studies, such as generative design and AlphaFold, as well as new TPD methods like PROTACs and similar degraders. We highlight important tools and examples. Additionally, we address current challenges, data limitations, and the complexity of designing PROTACs. We also look into ethical and regulatory concerns, including data privacy, AI transparency, and the evaluation of new methods, along with future perspectives.

Recent achievements, including AI-designed PROTACs that combine inhibition with targeted degradation, showcase the benefits of these technologies working together. Our aim is to give a complete overview of various therapeutic areas.

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I. INTRODUCTION

The process of finding new drugs the traditional way takes a lot of time, and it is also very expensive as well as very inefficient. A new drug typically takes more than ten years and costs about a billion dollars on the average to be approved and sold, and only around 10% of drugs that are evaluated in clinical trials eventually get approval. The high rates of failures (usually because of safety concerns or lack of efficacy) and the not very high rates of hits from the high-throughput screening methods make it possible that some of the targets, especially the “undruggable” proteins may be left dormant. To unlock these potential new areas of drug development, two monumental methods have surfaced. First, the AI and ML will be used to speed up the entire process of drug development significantly, namely, by sifting through giant biomedical datasets, predicting molecule characteristics as well as even creating new compounds. Second, the new TPD therapy will be called a new therapeutic paradigm; instead of stopping the disease protein action by the use of degraders, the selective elimination of the disease protein through the use of the cell's cleanup system is induced. TPD can eliminate pathogenic proteins (including those that have even the very powerful ones previously considered undruggable) by abducting the ubiquitin – proteasome or the lysosomal pathways. In this paper, earlier TPD and AI drug discovery paradigm (2019–2025) have been reviewed. We do the following: provide background on both areas, acknowledge the cutting-edge techniques and platforms, and discuss how these innovations, together, are making it possible to discover new drugs in new ways. The process of finding new drugs the traditional way takes a lot of time, and it is also very expensive as well as very inefficient. A new drug typically takes more than ten years and costs about a billion dollars on the average to be approved and sold, and only around 10% of drugs that are evaluated in clinical trials eventually get approval. The high rates of failures (usually because of safety concerns or lack of efficacy) and the not very high rates of hits from the high-throughput screening methods make it possible that some of the targets, especially the “undruggable” proteins may be left dormant. To unlock

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II. REVIEW OF LITERATURE

➢ *Drug Discovery Powered by AI*

The drug development process is now entirely dominated by the use of machine learning (ML) and artificial intelligence (AI). Figure 1 shows a typical AI-powered workflow: AI aids in target discovery, virtual screenings, hit generation, lead optimization, and even clinical trial organization. Deep neural networks, graph neural networks, transformer models, and reinforcement learning are examples of AI techniques. These models may predict protein architectures, binding affections, ADMET (absorption, distribution, metabolism, excretion, and toxicity) qualities, and many other things by learning from large chemical and biological datasets. The drug development process is now entirely dominated by the use of machine learning (ML) and artificial intelligence (AI). A standard AI-powered workflow is depicted in Figure 1: AI helps in the identification of targets, virtual screenings, generating hits, optimizing leads, and even organizing clinical trials. Deep neural networks, graph neural networks, transformer models, and reinforcement learning are examples of AI techniques. These models are capable of learning from huge chemical and biological datasets to forecast protein structures, binding affections, ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, and many more.

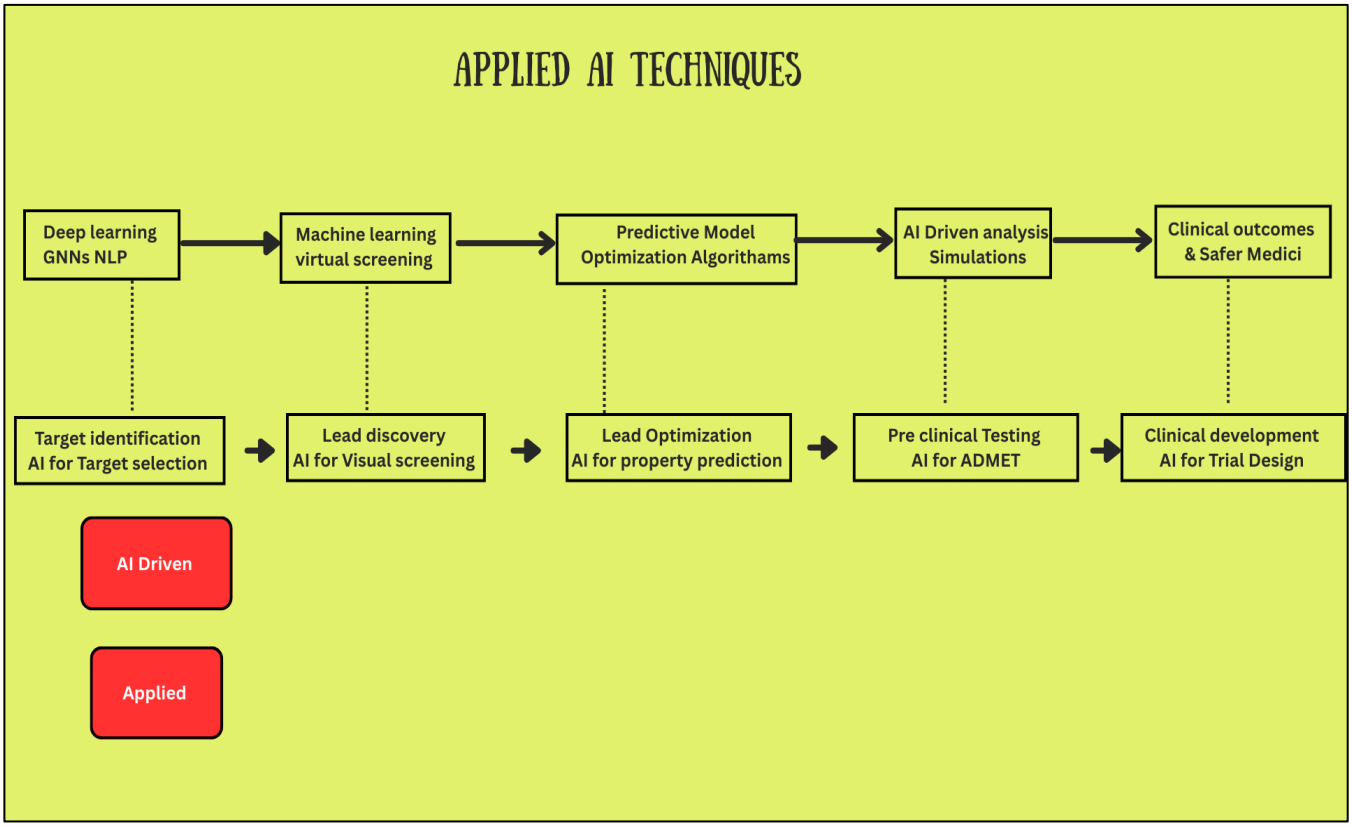

Fig 1. A Schematic AI-Powered Drug Discovery Pipeline, Merging Data from Genomics, Phenotypic Screens, and Chemistry to Speed Up Target Identification, Hit Discovery, and Optimization.

Deep learning and generative models are particularly powerful. As an illustration, GANs and VAEs are among all the techniques that have successfully been used to produce new molecular structures with desired characteristics. Structure prediction AI, such as AlphaFold, has been making waves in research by offering almost lab-like protein

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models. Virtual screening is also benefiting from such advancements: the use of convolutional neural networks enables the processing of millions of compounds in search of possible binders much quicker than traditional high-throughput screening. One example is the AI platforms that, within 18 months, pointed to a new candidate for idiopathic pulmonary fibrosis, which is very fast compared to classic timelines. The same goes for Atomwise's AI that predicted drug leads for Ebola in under a day. The AI's performance is not limited to drug repurposing and optimization: a classic example is given by the case of the BenevolentAI system that took the JAK inhibitor, baricitinib, as a COVID-19 treatment, thus getting emergency use authorization. Many companies and tools have shown this transition. Insilico Medicine's Chemistry42 platform applies deep generative chemistry for the synthesis of new inhibitors. To molecular modeling, deep learning frameworks like DeepChem and TorchDrug provide the necessary libraries. Reinforcement learning techniques (e.g. AlphaChem) and adaptive Monte Carlo algorithms are utilized for the probing of chemical space. Drug-like molecules can be produced with the help of transformer-based language models which have been trained on chemical SMILES strings. High-quality data, lack of bias, and confirmation of predictions are among the main problems that are common to all these methods. According to recent reviews, data curation and multi-task learning are the two main factors that can significantly enhance model robustness . The practical implementation of these approaches also requires meticulous cross-validation and an understanding of AI "black box" problems.

➢ *Targeted Protein Degradation (TPD)*

Targeted protein degradation is an innovative treatment approach that not only stops the function of the protein but also eliminates it by using the cell's waste disposal system. The most developed TPD form is PROTACs (proteolysis-targeting chimeras): a new class of drugs that consist of two small molecules that are connected. A specific protein (POI) is bound by one end of the PROTAC, and an E3 ubiquitin ligase is attached to the other end. When the two are connected, the PROTAC triggers the POI's ubiquitination, which signals it to be taken away by the 26S proteasome. The PROTAC then remains connected to the target protein, and the cell actively reuses the PROTAC to destroy more proteins.

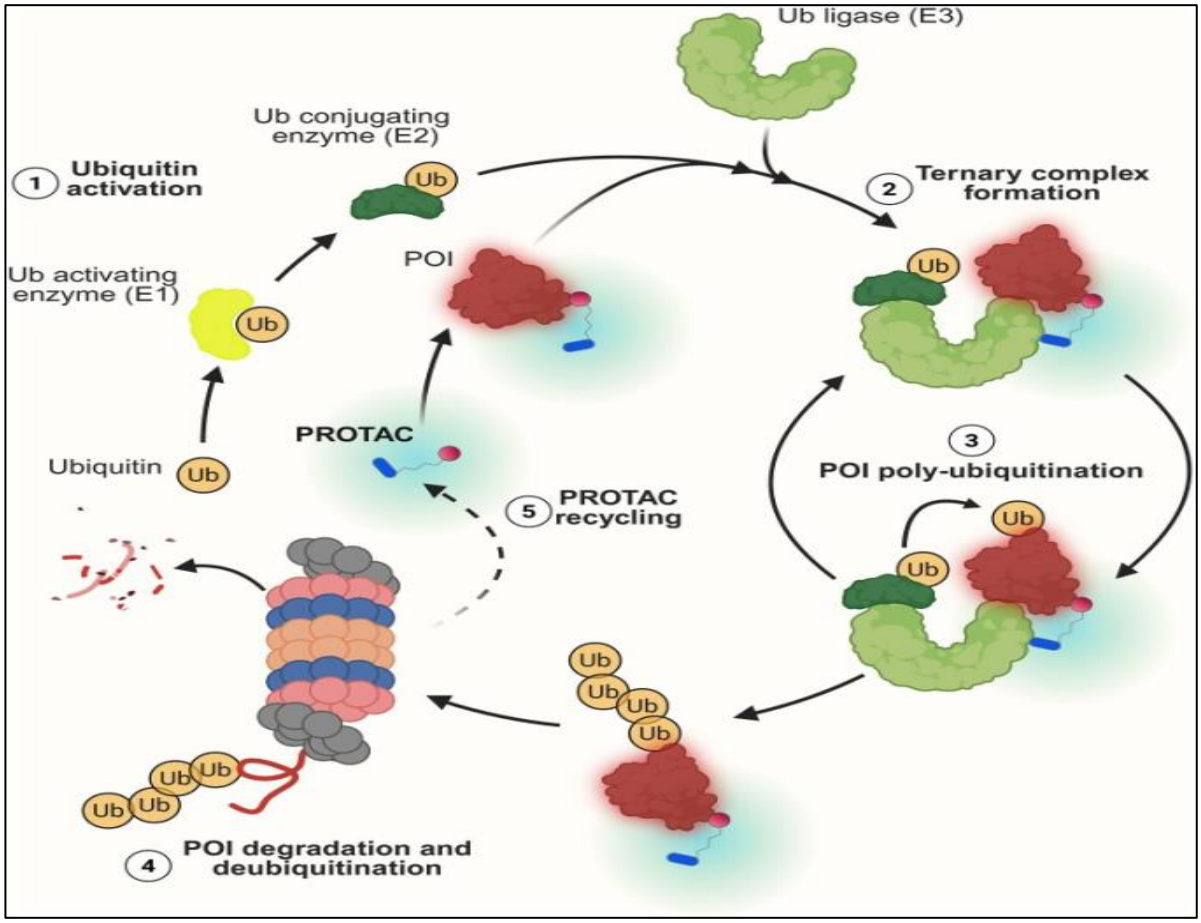

Fig 2. Mechanism of PROTAC-Mediated Degradation . A PROTAC Links a Target Protein (Red) to an E3 Ligase (Green), Promoting Target Ubiquitination and Proteasomal Degradation . Once the Target is Destroyed, the PROTAC can be Recycled.

The "undruggable" targets (such as transcription factors, and scaffolds) can be degraded using PROTACs as they only need a binding site and not an active site. On the other hand, molecular glue degraders (like thalidomide analogs) are less complex monovalent compounds that either create or maintain a protein–E3 interaction. Different lysosomal-targeting techniques (such as LYTACs for extracellular proteins) and autophagy-based methods

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(AUTACs) continue to broaden the idea of target accessibility through various methods.

The TPD toolkit has become vastly larger in a short period of time due to recent happenings and there are still more things to come. The huge number of PROTACs count that has been reported for the cancer targets alone has reached hundreds, with some of them already being tried out on humans. Among the mentioned ones the progesterone PROTAC ARV-471 receptor and the PROTAC ARV-110 androgen receptor have both made it up to the third stage of trials—this is a strong reference to the potential for the technology to be applied in practice. One such powerful application of AI is highlighted in a recent Nature Communications paper: Wang et al. (2025) teamed up with Insilico's Chemistry42 platform and produced a brand new small-molecule binder of the kinase PKMYT1, thereby creating a "dual-acting" PROTAC (D16-M1P2) which is the first in class and does both degrading and inhibiting of PKMYT1. This PROTAC not only revealed considerable but also long-lasting suppression of tumors during in vivo experiments, which is an indication of how effectively AI can speed up the process of designing complex degraders. In addition, other AI-based research works have begun making use of machine learning to forecast the formation of ternary complexes, choose linkers, and assess cell permeability for PROTAC candidates.

The area of oncology has already received much attention, but in addition TPD is also being looked into for infectious diseases, neurology, and other fields. To illustrate, certain types of BacPROTACs and hydrophobic tagging (HyT) approaches are showing potential with the bacteria causing infections. In summary, the published works are showing that TPD is having a "glorious era" characterized by fast discovery, which is made possible by the use of both chemistry and computer algorithms.

III. METHODOLOGY

In order to craft this review, we carried out an organized literature search of peer-reviewed journals, preprints, and recognized reports from the years 2019 to 2025. The search was conducted across different databases (PubMed, Web of Science, arXiv) by using keywords like "machine learning drug discovery", "AI drug design", "PROTAC", and "targeted protein degradation". Both experimental and review articles were included in the search. The publication we considered relevant had various AI/ML techniques (models, input data types, applications) and TPD strategies (degrader types, targets, and design principles) in them. The data was then arranged according to the themes like (e.g. AI in virtual screening, AI in synthesis; PROTAC linker design, PROTAC E3 selection) so that comparative analysis could be done. Just like with the previous systematic reviews, we created a table for the details of the studies, which helped us to recognize the ongoing trends and knowledge gaps. Key findings were divided into three main sections: technology, challenges, and outlook. No original experimental data were produced; instead, this work is based on a comprehensive narrative synthesis of published literature.

IV. CHALLENGES

- *Data and Model Limitations (AI).*

The choices of AI methods rely significantly on the quality and quantity of data. The drug discovery process often involves datasets that are noisy, skewed toward some chemotypes, and incomplete (e.g., a limited number of negative results are made public). These factors can result in overfitting and poor generalization. Data accessibility and model interpretability have been highlighted in recent reviews as persistent gaps . For instance, many machine learning models for activity prediction are highly accurate on a specific chemical series but do not perform well on new scaffolds.

Providing varied and reproducible training data (which also includes negative assays) is, therefore, a necessity. Another issue is model interpretability: "black-box" networks make it difficult to provide reasons for predictions, thereby complicating medicinal chemistry decisions and trust from regulators. The use of physics-based constraints or attention mechanisms can be of assistance, but comprehensive explainability remains a challenge. Computational cost and scalability are also factors, as complex models (like transformer-based chemistry models) require a lot of computing resources.

Biological Complexity and Gap in Translation. AI predictions most of the time are not taking into account biological context. A molecule which is predicted to have a target binding might not succeed because of its poor cell penetration, metabolic instability, or high toxicity. AI can help in modeling ADMET properties, but in vitro and in vivo testing are still very important. Also, AI designed drugs have hardly ever been successful in clinical trials (except for a few cases as Insilico's programs), which points to a gap in translation. Acceptance of AI results by regulatory agencies for submission (e.g. IND applications) is a rigorous validation process. These difficulties demand "Good Machine Learning Practice" frameworks and also the presence of humans in the decision-making process.

PROTAC Design Complexity. Each of the TPD modalities has its own limitations. The development of efficient PROTAC demands a combination of several factors that are interdependent: selecting a druggable target, picking the correct E3 ligase ligand, designing a linker with a stable ternary complex, and making sure the drug has good pharmacokinetics. For instance, many PROTAC candidates do not come up to the mark not on account of weak binding but because the ternary complex is either unstable or non-cooperative. Only a few E3 ligases (notoriously CRBN and VHL) are commonly used, partly because of less binder availability; going past these requires the discovery of new ligands and an understanding of tissue-specific E3 expression. PROTACs are usually big and polar, which may cause a decrease in cell permeability and oral

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bioavailability. It is very difficult to do this balancing act without losing the degradation potency.

Pharmacological and Safety Challenges. One of the big issues with off-target degradation is that it might happen with an indiscriminate degrader that could possibly take away critical proteins thus causing toxicity. The long-term impacts of gradual protein knockdown are still not fully known. When it comes to molecular glues (for example, immunomodulatory drugs) history has shown us with thalidomide's teratogenicity that there might be unforeseen risks. PROTACs can possibly activate the immune system or interfere with proteasome activity. Selectivity profiling and safety testing need to be done very carefully.

Ethical and Regulatory Issues (AI). The question of ethics is one of the major concerns in the area of AI technology as it relates to data privacy, bias, and the whole issue of responsibility. The data that is derived from patients (e.g., genomics used in target ID) has to be properly managed through consent and security. If there is an algorithmic bias (e.g., training on data from one population), it may worsen the situation regarding health equity. Ethical frameworks by specialists point out the fundamental principles of autonomy, justice, non-maleficence, and beneficence for AI in drug R&D. The openness (through algorithms being public, clear reporting of AI's decision logic) and accountability practices are essential to trust-building.

The Evaluation of AI and Degraders by Regulatory Bodies. Innovative technologies like these are slowly being considered by the regulatory authorities. The FDA’s recent position paper on AI in medicine development makes it clear that there should be no compromise on data transparency, model interpretability, and rigorous checks and validations. The EMA in Europe echoes this concern saying that the integrity of the data and the involvement of a human are the other two major issues at the stage of clinical trials. The matter of ownership of the resulting invention, in this case, an AI-generated molecule, is also important when it comes to patent rights. Current patent offices (like USPTO, EPO, UKIPO) usually do not accept AI as an inventor, thus making companies take a different approach to their IP strategies.

At TPD, there are still no approved medications belonging to this class, thus the guidelines are still in the process of forming. New molecular entities were represented by first-generation protein degraders such as fulvestrant, the drug that degrades estrogen receptors. PROTACs will be viewed in the same light as new chemical drugs and will, however, have their effects scrutinized based on the specific mechanism of action. It is very likely that the safety assessment would entail proving that the non-selective degradation does not lead to the overload of the proteasome pathways. With more PROTACs entering the late-stage trials (e.g. ARV-471), the regulators will be more experienced. To conclude, both AI tools and new modalities such as PROTACs will require early dialogue with regulators to set the right standards and to make sure that patients are safe.

- *Aspects of Ethics and Regulation*

Drug discovery and artificial intelligence provide unique ethical challenges. Patient data (genomic, clinical records) which are utilized for target discovery or predictive models must adhere to strict privacy and consent protocols. Bias mitigation is of utmost importance: for instance, if an AI model is trained only on data from one ethnic group, then it might produce less effective drugs for others, thus conflicting with ethical justice. Transparency and explainability are increasingly being demanded: open datasets, pre-registering AI methods and providing model rationales are all in line with the ethical principle of beneficence. Various authors have suggested governance frameworks that focus on informed consent, algorithmic accountability, and monitoring for AI-induced harms.

On the regulatory side, agencies are taking a proactive approach and changing their ways. The US FDA and the EU EMA have given out instructions on "Good Machine Learning Practices" and have been promoting the complete writing down of AI models, validation studies, and risk assessments as part of the good practice. For instance, the FDA's 2023 talk emphasizes that the predictions made by AI in a drug submission must be transparent and reproducible. Surely, AI-powered patient selection or trial designs must still pass through the ethical review and informed consent process in clinical tests. Moreover, liability is an issue: if a harmful decision made by AI prompts the question, who will be held accountable – AI developers, medical doctors or trial sponsors?

Targeted protein degraders as well as the issues of ethics and regulation are closely intertwined. TPD simply does not bring up new ethical matters that are very distinct from those associated with the use of other new drugs, however, its novelty calls for regulatory considerations. Regulators are likely to be very much concerned with the effects on other targets and the introduction of new toxicities. As an example, TPD might deactivate proteins whose roles are not known yet; therefore, it is necessary to perform extensive nonclinical safety studies. The development of “rapidly acting” therapies (for example, a PROTAC that takes out an oncoprotein at once) is one of the areas that pervade the field of personalized medicine and it is also a requirement for extensive testing. Patent problems are an issue: since PROTACs consist of two binding ligands, firms have to patent not only the ligands but also the linker and the entire degrader. Inventions of new IP strategies or collaborative agreements are often the result of this area. Finally, access to medicines is a big ethical issue that is going to be around for a long time: while we are working on making, more user-friendly, AI-designed therapeutics and TPD drugs, it is important to ensure that the innovations are made available to all the patients in the world and not just the ones in the rich healthcare systems.

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V. FUTURE ASPECTS

In the near future, AI and TPD will definitely mix giving birth to increasingly powerful applications. In the case of AI, we already see the next-gen models (large language models trained on chemical data, self-supervised graph learners) coming. This could make it possible to design drugs totally new by building up the whole chain from genotype to phenotype. The application of AI to the integration of multi-omics data (genomics, proteomics, phenotypic screens) will facilitate more reliable target validation. Robotics and high-throughput experimentation ("self-driving labs") will link the stages: AI-generated hypotheses can be swiftly confirmed in automated systems, reaching toward the most promising leads. Quantum computing, although still in its infancy, might one day apply to molecular simulation problems that are currently considered impossible to solve. The good news is that as AI becomes more commonplace, the number of free tools and open-access databases will also grow, thereby accelerating the process of innovation globally.

New and exciting horizons are opening up in the field of TPD. The new E3 ligases other than the habitual ones like CRBN/VHL will be utilized thus making tissue-specific degradation possible. The application of molecular glues to many targets will be possible as chemists are likely to discover more small bioactive molecules that stabilize the target–E3 interactions, thus making the process easier. The "dual" or multi-functional degraders idea (such as in the D16-M1P2 PROTAC) will expand: the compounds that both restrict and eliminate eventually lead to total target suppression. On the other hand, TPD strategies will also go beyond proteins: PROTACs or RIBOTACs (targeting RNA for degradation) based on oligonucleotides are in the process of being developed which would probably make it possible to get rid of both pathogenic RNAs and misfolded proteins.

Combining different modalities is yet another trend of the future. Current debates talk about maturing the WIN concept by coupling immune checkpoint inhibitors or kinase inhibitors with procarbazine to defeat resistance. And AI will be heavily involved in this process. One could picture AI systems that propose the whole strategy of degradation: from the selection of a pathway's optimal target to the design of the E3-recruiting warhead and linker. A recent Nature Communications publication has showed this kind of AI-oriented PROTAC pipeline very clearly. Also, machine learning could predict which patients would get the most benefit from specific PROTACs according to tumor genomics and proteostasis networks.

The regulatory and ethical frameworks must not lag behind. We expect more detailed rules for AI validation comparable to those for drug validation, and official routes for AI-labeled drug candidates. For TPD, it is likely that the interactions between developers and agencies at the early stages will be very similar to the guidance already given for gene and cell therapies. The ongoing discussions between chemists, biologists, AI experts, and ethicists will be a safeguard against the misuse of these powerful technologies.

In conclusion, biological and computer advancements will work together to identify new drugs in the future. The focused degraders will only contribute to the medication development process; artificial intelligence will be the one to advance and play a significant role in investigating the extent of the chemical. In the end, these two developments will usher in a new era of medications that are efficient, patient-specific, and selective.

VI. CONCLUSION

The whole process of drug discovery is changing dramatically. In fact, AI has become one of the most important factors in modern pharmaceutical R&D by offering faster discovery and new drug candidates besides being a rare research tool in the past. At the same time, targeted protein degradation has given rise to new therapeutic avenues even for previously impossible targets, and now several PROTACs are at the last stage of trials. Through our review, we have shown that the developments in both areas are very much interdependent: AI contributes to the design of complex degraders (as in the AI-designed PROTAC example), whereas the introduction of new drug forms raises the question of novel computational challenges.

Nonetheless, considerable voids still exist. Guaranteeing data quality, model transparency, and chemical tractability are continuous hurdles. Ethical and legal frameworks need to advance to regulate artificial intelligence (AI) methods and next-generation technologies. The barriers are to be overcome—via open science, teaming up across disciplines, and stringent validation—the combined forces of AI and TPD can be employed to provide safer and more effective therapies. Thus, the fusion of data-driven algorithms and protein-degradation biology signals a complicated but promising future for drug discovery.

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