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TARGETED DEGRADATION OF EXTRACELLULAR PROTEINS: EMERGING STRATEGIES AND THERAPEUTIC POTENTIAL

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ABSTRACT-

Extracellular protein degradation by targeted degradation approaches is an area that is growing in significance as an extension of the existing methods of targeted protein degradation to enable selective degradation of extracellular disease targets that are inaccessible through proteasome-mediated protein degradation approaches. The purpose of this review was to assess the biology of extracellular protein degradation, platforms of degradation, therapeutic use cases, translational benefits, existing limitations, and current trends in the field of extracellular protein degradation. A thorough literature review was conducted on different aspects of extracellular protein degradation including lysosome targeting chimeras, antibody degrader technology, cytokine receptor targeting chimeras, small molecule technology, and extracellular vesicles. The presented evidence clearly indicates that internalization via receptors and lysosomal targeting constitute the core mechanism of extracellular protein degradation. LYTACs have been established as the most well-characterized system, although novel approaches such as macromolecules, small molecules, and vesicles may offer more flexibility in terms of targets and delivery. Possible uses may be for the treatment of cancer, inflammation, neurodegenerative diseases, among others where extracellular protein-mediated pathology occurs. Limitations include issues regarding the presence of the required receptor, biodistribution, pharmacokinetics, immunogenicity, off-target degradation, difficulty in manufacturing, and insufficient clinical evidence.

Keywords: Extracellular protein degradation, LYTACs, Lysosomal degradation, Targeted protein degradation, Therapeutic targeting

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Introduction

Targeted protein degradation has become an important approach in therapeutics due to its focus on getting rid of the disease-causing proteins, rather than just inhibiting them. The reason for such importance lies in the fact that many drugs act based on the occupation of a functional binding site for long periods of time, while degradation-based therapies can have persistent biological effects even after the initiation of protein removal. Event-based pharmacology has increased the attention paid to the proteins which were thought to be undruggable before and has become more important in cancer and other diseases (Hinterndorfer et al., 2025). The evolution of therapeutics in general is also based on the idea of influencing various cellular events and not just acting on receptors and enzymes. One example of such influence is therapeutic modulation of regulated non-apoptotic cell death, which shows how the control of intracellular pathways can become another way of treatment (Hadian & Stockwell, 2023). In spite of these developments, a large number of existing targeted protein degradation systems rely on intracellular protein degradation machinery like the ubiquitin-proteasome pathway. This makes it impossible to use these methods directly for extracellular proteins, secreted molecules, and other membrane-bound proteins. The same situation prevails in other therapeutic scenarios where the intracellular nature or complicated structure makes it impossible to intervene using conventional methods. Protein-protein interaction targets like the KEAP1-NRF2 interaction, for example, may need special approaches since the active sites of these molecules are often hard to manipulate using traditional small molecules (Crisman et al., 2023). These challenges have prompted researchers to explore other degradation mechanisms, specifically autophagy-lysosome-mediated degradation pathways (Cassidy & Zhao, 2023).

However, extracellular and membrane-related proteins are of high significance because they act in signaling, tissue organization, inflammation, tumor progression, and intercellular communication. For instance, the extracellular matrix is important because its makeup and remodeling affect cancer cell behavior, invasion, and therapeutic responses (Huang et al., 2021). Another example is provided by extracellular vesicles, which help in cell-cell communication and carry biologically active compounds that impact disease progression and therapeutic processes (Han et al., 2024). Moreover, biofilms are another example showing how complex extracellular structures affect the persistence of therapeutic action and reduce its efficiency, thereby highlighting the importance of approaches to therapeutic intervention targeting not only intracellular but also extracellular and intercellular processes (Jiang et al., 2020). Furthermore, other extracellularly important therapeutic systems such as those based on microRNAs in tissue injury illustrate the importance of modulation of biological pathways (Giordano et al., 2020). This has resulted in the rise of extracellular targeted protein degradation, a process whereby extracellular or membrane proteins are diverted towards internalization and lysosomal degradation. Receptor-mediated endocytosis and lysosomal trafficking serve as the biological backbone of this mechanism, whereby the target proteins can be harvested externally and eventually sent to the cellular compartments responsible for their degradation. At the same time, new methods of drug delivery are being developed to enhance the recognition and delivery of the therapeutic molecules into the cells. The peptide-functionalized nanocarriers serve as an example of how artificial targeting ligands can help improve selective delivery and develop advanced therapies (Buddhiraju et al., 2024).

Thus, modern advances in this field clearly demonstrate that there was a shift from conventional intracellular degraders to the extracellular degradation technologies that are more diverse. However, some problems should be discussed as well. They include receptor selection,

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biodistribution, pharmacokinetics, tissue specificity, safety, and manufacturing. All these aspects are relevant given the fact that extracellular proteins are usually distributed all over the body and perform physiological functions. As for more research on therapeutics, it is obvious that good therapy is a balance between targeting molecules and ensuring safety, which is proven by the attempts to use native protection proteins such as catalase (Anwar et al., 2024). Consequently, this review attempts to critically assess the biological underpinnings, degrader platforms, clinical applications, comparative advantages, translational hurdles, and future trends in the targeted degradation of extracellular proteins. It also identifies current gaps and future directions in the development of clinically relevant targeted degradation of extracellular proteins.

2. Methodology

This study employed a comprehensive review approach to summarise the existing literature on targeted degradation of extracellular proteins for therapeutic applications. The peer-reviewed journal papers, scholarly books and conferences proceedings from the scholarly databases and Google Scholar, ScienceDirect and DOAJ were used to search for relevant literature. Papers that did not have any relation with targeted protein degradation or only dealt with conventional intracellular degradation not relating to extracellular degradation were excluded from this study. Keyword approach was employed to search for relevant literature using combinations of keywords including but not limited to targeted extracellular protein degradation, extracellular protein degrader, lysosome-targeting chimera, LYTAC, lysosomal degradation, membrane protein degradation, cytokine receptor-targeting chimera, KineTAC, antibody-based protein degradation, small molecule extracellular protein degrader and extracellular vesicle-mediated degradation. The identified studies were first screened for their relevancy using their titles and abstracts, then their complete texts were assessed for inclusion. Relevant studies were further grouped and thematically categorized under biological mechanisms, degrader technologies, potential therapeutic targets, advantages of different degrader technologies, translational hurdles, and new developments. The synthesis approach entailed comparative analyses of results in relation to these themes to draw out consistent biological mechanisms, technology differences, therapeutic prospects, limitations, and research areas that need to be addressed. Figure 1 provides an overview of the entire comprehensive literature review process.



Figure 1. Overview of the Comprehensive Review Process

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3. Results

From the literature review, it was clear that extracellular targeted protein degradation has become a distinct form of the traditional targeted protein degradation method, with a focus on lysosomal trafficking, receptor-mediated endocytosis, extracellular and membrane protein target elimination, and new forms of degrader. The findings have been classified into seven broad categories ranging from biological principles to LYTACs, macromolecular degraders, small molecule, and extracellular vesicles-based degraders.

3.1 Biological Basis and Evolution of Extracellular Targeted Protein Degradation

Targeted protein degradation in the extracellular space extends the methods of protein degradation beyond intracellular substrates through the utilization of the mechanism of receptor-mediated entry, endosomal transport, and lysosomal degradation. Such a strategy allows for the degradation of secreted proteins, membrane receptors, and other extracellular substrates that are out of reach for proteasomal-based degradation systems. Differences between proteasomal and lysosomal degradation are shown in Table 1.

Table 1. Biological Features of Proteasomal and Lysosomal Targeted Protein Degradation

Feature	Proteasomal Degradation	Lysosomal Degradation	References
Main target location	Primarily intracellular proteins	Extracellular, membrane, and internalized proteins	(Ding et al., 2020; Zhao et al., 2022)
Major degradation machinery	Ubiquitin–proteasome system	Endosomal–lysosomal pathway	(Paudel et al., 2023; Tsai et al., 2024)
Entry requirement	Intracellular accessibility	Receptor-mediated internalization	(Lin et al., 2021; Chen et al., 2023)
Suitable substrates	Mainly soluble intracellular proteins	Secreted proteins, receptors, and larger membrane proteins	(Wells & Kumru, 2024; Mamun et al., 2025)
Main therapeutic advantage	Efficient intracellular protein removal	Access to previously inaccessible extracellular targets	(Samarasinghe & Crews, 2021; Zhu et al., 2025)

3.2 LYTACs and Receptor-Mediated Lysosomal Degradation

LYTACs are one of the best-known methods of extracellular targeted protein degradation. They are bifunctional compounds that combine both a disease-causing extracellular or membrane protein and a lysosome trafficking receptor, enabling the endocytosis of the receptor and lysosomal degradation of the target. The initial design of LYTACs showed the ability of targeting of extracellular proteins and cell surface receptors, which are out of reach of traditional proteasome-

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dependent degraders, toward lysosomes (Banik et al., 2020). Further research has allowed developing more complex LYTACs involving different internalization receptors and tissue-specific systems, including those that use receptors expressed selectively in certain organs to increase degradation selectivity (Lin et al., 2021; Chen et al., 2023; Li et al., 2025). Although LYTACs show great promise as therapeutic agents, the efficacy of LYTACs depends on various factors such as receptor abundance, internalization capability, degrader size, pharmacokinetics, and tissue distribution (Wells & Kumru, 2024; Mamun et al., 2025; Zhu et al., 2025).

LYTACs ensure the removal of extracellular proteins via receptor-mediated internalization and lysosome trafficking as shown in Figure 2.

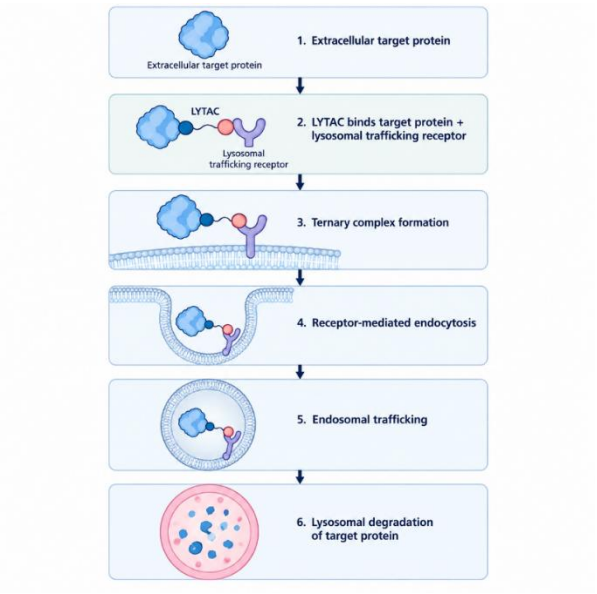


Figure 2. LYTAC-Mediated Protein Degradation

The stepwise LYTAC degradation pathway is exemplified by Figure 1, where the pathway starts with the identification of the extracellular target protein and its receptor. This complex then goes through endocytosis, followed by transport to the endosome and the lysosome where it gets degraded.

3.3 Antibody-, Cytokine Receptor-, and Macromolecule-Based Degrader Platforms

The antibody- and cytokine receptor-mediated degraders expand the concept of extracellular protein degradation through the fusion of target selectivity with cell internalization processes. While antibody-mediated systems offer target specificity by recognizing selective targets on the cell surface, cytokine receptor-mediated platforms make use of naturally occurring receptors that allow the uptake of proteins bound to them for lysosomal degradation. These systems offer excellent specificity and modularity, but there are factors that affect their efficacy, as shown in Table 2.

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Table 2. Major Macromolecule-Based Extracellular Protein Degradation Strategies

Platform	Main Design Principle	Target Type	Major Advantage	Main Limitation	Supporting References
LYTAC	Target binder linked to a lysosomal trafficking receptor ligand	Extracellular and membrane proteins	Direct lysosomal targeting	Dependence on receptor expression	(Banik et al., 2020; Li et al., 2025)
Antibody-based degrader	Antibody recognition combined with internalization machinery	Cell-surface proteins	High target specificity	Large molecular size and limited tissue penetration	(Sun et al., 2025)
Cytokine receptor-targeting chimera	Target-binding module linked to a cytokine receptor ligand	Surface and extracellular proteins	Efficient receptor-mediated internalization	Possible cytokine-related biological effects	(Pance et al., 2023)
Other macromolecular degraders	Engineered proteins or bifunctional biologics	Disease-associated extracellular proteins	Modular and adaptable design	Manufacturing and pharmacokinetic complexity	(Wells & Kumru, 2024; Mamun et al., 2025)

3.4 Small-Molecule and Extracellular Vesicle-Based Degradation Strategies

Small molecules and extracellular vesicles are other potential substitutes for large degrader proteins. While small molecules that have dual activity may exploit natural systems for extracellular clearance with benefits like lower molecular weight, better chemical versatility, and possible enhanced penetration of tissues compared to antibodies, extracellular vesicles take advantage of natural intercellular transportation with the capability to engineer them for target recognition and delivery. In spite of the success in developing small molecules for the induction of extracellular protein degradation, the ligand discovery, selectivity, biological stability, and pharmacokinetics improvement continue to be challenging (Caianiello et al., 2021; Chen et al., 2023). On the other hand, the natural biocompatibility, multivalent surface structure, and cargo modification capabilities make extracellular vesicles promising candidates for complex or multiple targets degradation tasks (Kumar et al., 2024; Yang et al., 2024). It is also evident that it is possible

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to develop systems based on extracellular vesicles that target multiple extracellular proteins, although the problems with production uniformity, biodistribution, quality assurance, and scalability still exist (Tong et al., 2026).

3.5 Therapeutic Applications of Extracellular Targeted Protein Degradation

Extracellular degradation technologies could find uses in many fields of medicine since a variety of disease conditions are characterized by involvement of secreted proteins, membrane receptors, extracellular signal molecules, and matrix-associated components. At present, cancer is an example of the most important field for such applications, although inflammation, immunity-related, neurologic, and other protein-based diseases might be candidates too. Some of these applications are listed in Table 3.

Table 3. Potential Therapeutic Applications of Extracellular Targeted Protein Degradation

Disease Area	Relevant Target Class	Potential Therapeutic Role	Supporting References
Cancer	Oncogenic receptors, growth factors, tumor-associated surface proteins	Removal of signaling proteins involved in tumor growth and resistance	(Dale et al., 2021; Chirnomas et al., 2023; Hinterndorfer et al., 2025; Sung et al., 2026)
Tumor microenvironment	Extracellular matrix proteins and matrix-associated factors	Modification of extracellular conditions supporting tumor progression	(Huang et al., 2021; Zhang & Zhang, 2025)
Inflammatory and immune disorders	Cytokines, cytokine receptors, extracellular inflammatory mediators	Reduction of pathogenic extracellular signaling	(Pance et al., 2023; Chen et al., 2025)
Neurological disorders	Pathogenic extracellular proteins and disease-associated receptors	Targeted removal of extracellular disease mediators	(Soares Martins et al., 2021; Yang et al., 2024)
Other protein-mediated disorders	Secreted and membrane-associated disease factors	Expansion of treatment beyond conventional inhibition	(Chen et al., 2023; Wells & Kumru, 2024)

3.6 Comparative Advantages and Challenges for Therapeutic Translation

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The extracellular targeted protein degradation technology provides a unique pharmacological feature since it involves degradation of the disease-causing proteins instead of inhibiting them. This event-triggered strategy can result in sustained biological effects and broaden drug treatment options in cases where there is no appropriate binding site in proteins (Samarasinghe & Crews, 2021; Zhao et al., 2022; Tsai et al., 2024). In addition, the available degrader technologies have their own merits: the ability to deliver the proteins into lysosomes using LYTACs, high targeting specificity using antibodies, the use of endogenous cytokine receptors, versatility of small molecules, and delivery of multiple drugs using extracellular vesicles (Pance et al., 2023; Wells & Kumru, 2024; Mamun et al., 2025). Nevertheless, clinical applications are restricted due to receptor availability, formation of ternary complexes, tissue penetration, pharmacokinetic properties, biodistribution, immunogenicity, and non-specific proteolysis. In consequence, most extracellular protein degrader methods are in an early stage of development compared to the intracellular targeted protein degradation tools (Chirnomas et al., 2023; Hinterndorfer et al., 2025).

Figure 3 highlights the major benefits and translational challenges of the extracellular targeted protein degradation strategy.

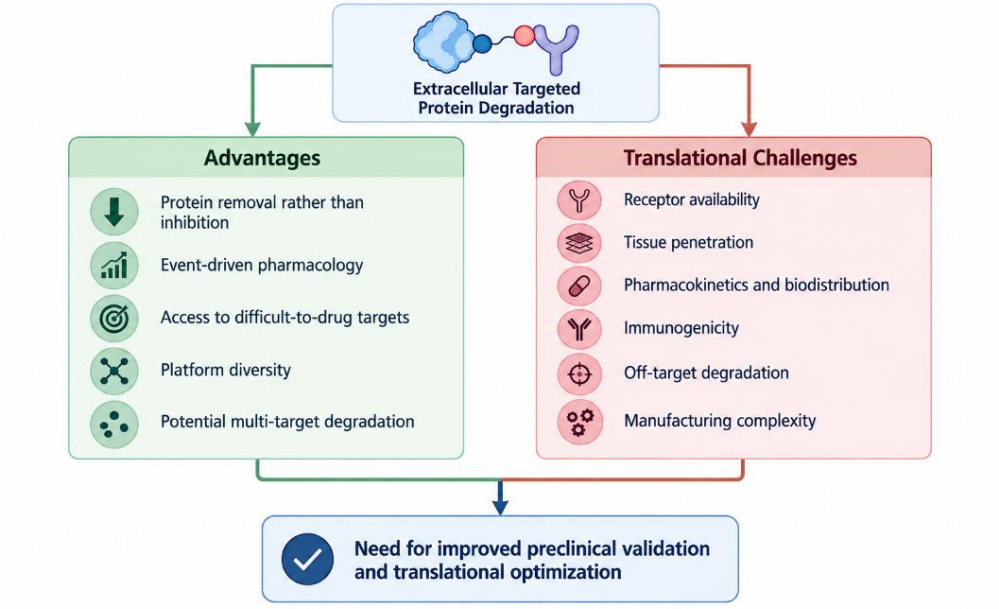


Figure 3. Advantages and Translational Challenges of Extracellular Protein Degradation

The trade-off of extracellular protein degradation between its therapeutic efficacy and translational limitations is depicted in Figure 2. While such technologies offer direct elimination of the target protein and extended access to them, their clinical translation needs better development in terms of receptors, delivery, safety, pharmacokinetics, and production.

3.7 Emerging Trends and Future Directions

The future of this technology is headed towards achieving selective tissue degradation, internalization receptor diversification, degrader design miniaturization and modularity, multiple target approach, exosomal modifications, and disease-specific delivery methods. The next developments will also likely cover improvements in pharmacokinetics, biomarker selection,

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receptor targeting efficiency, and transformation of preclinical platforms into clinically useful treatments. The most important emerging trends are outlined in Table 4 below.

Table 4. Emerging Trends and Future Directions in Extracellular Targeted Protein Degradation

Emerging Trend	Expected Advantage	Major Research Need	Supporting References
Diversification of internalization receptors	Broader target and tissue coverage	Identification and validation of new trafficking receptors	(Pance et al., 2023; Li et al., 2025)
Tissue-selective degradation	Improved therapeutic specificity and safety	Exploitation of tissue-restricted receptor expression	(Wells & Kumru, 2024; Mamun et al., 2025)
Smaller degrader architectures	Better tissue penetration and pharmacokinetics	Development of potent extracellular ligands	(Caianiello et al., 2021; Zhu et al., 2025)
Antibody-based degradation	High molecular specificity	Improved delivery and scalable production	(Sun et al., 2025)
Multi-target degradation	Simultaneous removal of multiple pathogenic proteins	Control of selectivity and biological safety	(Tong et al., 2026)
Engineered extracellular vesicles	Multivalent and potentially tissue-directed delivery	Standardization, biodistribution control, and scale-up	(Kumar et al., 2024; Yang et al., 2024; Tong et al., 2026)
Clinical translation and biomarker development	Improved patient selection and treatment monitoring	Pharmacodynamic biomarkers and human validation	(Tsai et al., 2024; Hinterndorfer et al., 2025)

4. Discussion

From the analysis of the literature, it is clear that the concept of degradation of extracellular proteins is a promising development in the field of protein degradation therapy in that it expands the potential target space of this method from intracellular proteins to extracellular ones. Indeed, lysosome-directed technologies have been shown to be able to target secreted and membrane proteins by means of their internalization and targeting to lysosomes by means of receptor recognition. Compared to traditional drug design based on occupancy, lysosome-targeted degradation is a completely new approach. However, among the existing methods, LYTAC technology seems to play an especially important role due to the possibility of direct targeting of extracellular proteins via lysosome receptors. The above analysis agrees with the conclusions of Li et al. (2025).

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Another critical observation in the field relates to the increasing diversity of extracellular degrader platforms. Antibody-based systems, cytokine receptor targeting chimeras, dual-function small molecule, and extracellular vesicle-based systems offer various degrees of selectivity, internalization capability, tissue penetrance, and modularity. It is especially relevant because extracellular targets vary greatly in size, localization, concentration, and physiological function, and thus there is no likelihood that one universal platform would be sufficient for all cases. This idea is also supported by the general expansion of targeted protein degradation techniques. In their review, Zhong et al. (2024) note how current degradation technologies evolve from classical protein inhibition and become an integral part of the drug discovery pipeline. Here, this notion is expanded by adding that extracellular protein degradation can expand the druggable proteome even further through lysosomal and receptor-mediated clearance.

In cancer research, the significance of extracellular degradation is clearly seen through the involvement of membrane receptors, secreted signaling molecules, and extracellular signaling pathways in the development and drug resistance of cancer. Extracellular vesicle-based technologies might play an important role in this scenario as a result of the presence of biological transportation capability and the possibility of engineering the targets. According to Lin et al. (2022), mesenchymal stem cell-derived exosomes play a key role in cancer therapy resistance, which proves the strong influence of extracellular vesicle biology on the effectiveness of the therapy.

In addition, the results may be significant in fields outside oncology. Since extracellular proteins have roles in processes like inflammation, tissue repair, metabolism, and intercellular communication, there may be ways to develop extracellular protein degradation techniques for various diseases in the future. Zhou et al. (2024) revealed that extracellular vesicles derived from adipose-derived stem cells could modulate inflammation and tissue repair. Similarly, Xiao et al. (2024) highlighted that modulation of diseases usually occurs in an interconnected pathway and is impacted by extracellular components. Therefore, extracellular protein degradation techniques in the future may have to take into account broader biological systems rather than just individual extracellular proteins.

However, there is no denying the presence of many limitations associated with this technology. In the majority of cases, extracellular degraders are mainly based on preclinical and proof-of-concept data. It is possible that receptor availability, target protein tissue specificity, degrader stability, biodistribution, immunogenicity, off-target degradation, and manufacturing challenges might limit the clinical potential of extracellular degrader technologies. Comparisons of different platforms are not easy to do as well due to the usage of different target proteins, models, and metrics of degradation efficiency. The long-term safety and the implications of extracellular protein depletion have not been thoroughly investigated yet.

Thus, future research should be directed at developing tissue-specific internalization receptors, designing more stable degrader constructs with reduced size, establishing standards for evaluating degradation efficiency, and performing validation in vivo. Comparative analysis of various degrader formats, optimizing pharmacokinetics, selecting qualified biomarkers as target proteins, and studying immune and off-target effects are also required.

5. Conclusion

The breakdown of extracellular proteins is one of the relatively new fields in the science of targeted protein degradation, through which one can achieve selective degradation of extracellular proteins of various types connected with different diseases. Instead of inhibition, such approaches use the degradation of proteins through their uptake using receptor-mediated endocytosis followed by lysosomal degradation, thereby increasing the range of targetable proteins. Currently, LYTACs are one of the most advanced methods for degradation of extracellular proteins, whereas antibodies, cytokine receptors, small molecules, and extracellular vesicles are developing as new platforms. They may become highly relevant for the treatment of cancer, inflammatory diseases, neurodegenerative diseases, among others, in which the extracellular signaling protein or the membrane receptor is implicated. However, it is true that there are numerous translational challenges that must be solved in relation to the availability of the receptor, the ability to penetrate tissues, pharmacokinetics, biodistribution, immunogenicity, off-target effects, manufacturability, and lack of clinical data. The field, therefore, remains highly preclinical in spite of the tremendous technological advances made. Future research in the field requires the identification of receptors for selective internalization, designing of smaller and stable degradation scaffolds, improving of delivery efficiencies, standardization of degradation measurement, and identifying pharmacodynamic biomarkers. Overall, extracellular protein degradation holds huge promise to expanding the drug-targetable proteome; yet, future success depends on proper balancing between molecular and biological specificity with efficient delivery.

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