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LYSOSOME-TARGETING CHIMERAS FOR NEXT-GENERATION DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT

Lysosome-targeting chimeras (LYTACs) are emerging as a versatile targeted protein degradation strategy for extracellular, soluble, and membrane-associated proteins that remain difficult to address with conventional inhibitors. These bifunctional constructs connect a disease-associated target to an internalizing lysosome-shuttling receptor, promoting endocytosis, endosomal sorting, and lysosomal destruction. This review examines the molecular mechanisms, architectural components, receptor systems, linker designs, and discovery strategies governing LYTAC activity. It also evaluates developing applications in cancer, immune-mediated disorders, fibrosis, metabolic disease, neurological conditions, and infectious diseases. Antibodies, peptides, aptamers, small-molecule ligands, tissue-selective receptor binders, and engineered delivery systems provide expanding opportunities to improve target recognition and cellular specificity. However, variable receptor expression, incomplete understanding of intracellular trafficking, inconsistent degradation efficiency, limited bioavailability, immunogenicity, and non-standardized assays continue to restrict translation. Future progress will depend on programmable tissue-selective platforms, robust pharmacokinetic–pharmacodynamic evaluation, validated biomarkers, scalable manufacturing, and rational combination treatments. Optimized LYTACs may ultimately convert previously inaccessible proteins into clinically actionable targets and broaden the therapeutic scope of degradation-based drug discovery.

Keywords: Lysosome-targeting chimeras, targeted protein degradation, lysosomal trafficking, drug discovery, precision therapeutics

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1. Introduction

Targeted pharmacology has been based on small molecules or biologics that inhibit protein function by maintaining effective occupancy. While this approach has led to transformative therapies, it is still limited by the requirement to have druggable binding pockets in the target, frequent drug exposure, and adequate and long-lasting suppression of the pathway. A majority of disease driving proteins are extracellular, conformationally complex, membrane-associated, and/or functionally redundant, which is why they are difficult to control using traditional inhibitors. Targeted protein degradation has changed this paradigm by taking the place of temporary inhibition with selective degradation of pathogenic proteins. Proteasome directed technologies, however, work primarily in the intracellular environment, and thus are not easily applicable to much of the secreted and cell-surface proteome. To break this barrier, extracellular or membrane-bound targets are targeted to endogenous endocytic receptors for lysosomal degradation through the use of lysosome-targeting chimeras (LYTACs), which enable pharmacologic targeting of targets in new biological compartments that would otherwise not be accessible (Zhou et al., 2025).

LYTACs are heterobifunctional molecules that consist of a target-recognition domain and a receptor ligand for the lysosome linked together by an appropriate linker. The target-binding part is used for binding the protein of interest, while the trafficking part is used to recruit an internalizing receptor that can be used for endosomal–lysosomal trafficking. This ternary complex facilitates endocytosis, endosomal sorting, and lysosomal proteolysis; and the trafficking receptor can be recycled back to the cell surface. This modular design allows for selective optimization of target affinity, receptor engagement, linker geometry, and cellular uptake (Zhou et al., 2026). Compared with occupancy-dependent antagonists, LYTACs can generate longer-lasting and more potent pharmacological effects by killing the target while it remains bound to the receptor, especially in cases where partial inhibition allows for the presence of some non-inhibited target and/or the capacity for the pathway to be reactivated quickly.

The selection of the lysosome-shuttling receptor plays a key role in tissue distribution, internalization efficiency and therapeutic selectivity. The cation independent mannose-6-phosphate receptor-directed systems are widely applicable to cells, while the asialoglycoprotein receptor-directed systems can enable hepatocyte-specific degradation. As the library of small-molecule receptor ligands grows, they can be smaller than large glycopolypeptide or antibody formats, offer better chemical definition, and be subject to medicinal-chemistry optimization (Yang & Zhu, 2025). However, several factors must be taken into account such as the density of the receptor, the rate of receptor recycling, the valency of the bound ligand and the intracellular trafficking if efficient delivery to the lysosomes is to be achieved.

The big promise of LYTAC technology is that it could make “undruggable” proteins, which are important for therapeutic purposes, accessible to rational drug development. These include catalytic-site inhibition-resistant disease-associated extracellular proteins, oncogenic receptors, adhesion molecules, immune-regulatory proteins, and soluble mediators. This degradation of abnormal membrane proteins can abate both enzymatic and non-enzymatic activity, diminish receptor recycling, and hinder compensatory signaling to promote the growth of malignancy in oncology (Zheng et al., 2024). These properties are particularly significant for heterogeneous tumours, where rewiring of adaptive pathways and continued expression of target proteins play a role in treatment failure and acquired resistance (Mao et al., 2026).

LYTAC development now includes antibodies, peptides, glycoconjugates, small molecules and constructs that are able to deliver. Despite their potential for sequence-level optimization, peptide-based recognition and trafficking modules have tunable affinity, relatively small size, and can be engineered to stay stable in the presence of proteases and are not exposed systemically (Wang et al., 2025). Chimeric agents can also be protected from degradation by nanocarriers and other drug delivery systems, their pharmacokinetics can be modified, they can accumulate in tumours and they can be coordinated to target engagement with receptor-mediated uptake (Lin et al., 2026). Lysosome-

centred nanomedicine also opens up the possibility of a synergistic effect of targeted degradation and controlled release, organelle modulation, imaging, and stimulus-responsive activation in the tumour microenvironment (Xu et al., 2026).

Although significant progress has been made, there are still significant translational barriers. The efficiency of degradation may depend on receptor expression, receptor target abundance, mobility of the membrane, endocytic pathway, capacity of the lysosomes, and disease-specific trafficking defects. Larger or very-multivalent constructs could find themselves with low tissue permeability, quick clearance, immunogenicity, manufacturing difficulty, or unwanted receptor activation. On the other hand, high affinity/over-occupancy can lead to problems with trafficking to the productive site and decrease catalytic turnover. Better pharmacokinetic–pharmacodynamic correlations, a degradation-selective biomarker, a standard assay, and comparative animal models are yet to be developed to discriminate between promising platforms and context-dependent experimental effects. Safety assessment should also clarify whether long-term elimination of abundant surface proteins is harmful to normal tissues or is it a factor in disrupting the lysosomal homeostasis.

A critical pharmacological synthesis is therefore needed to link molecular design to target choice, delivery characteristics, therapeutic effects and clinical feasibility. This review examines LYTACs as an emerging platform for next-generation drug discovery and development through three objectives:

- To explain design principles and lysosomal trafficking mechanisms underlying lysosome-targeting chimera technologies.
- To evaluate emerging LYTAC platforms for degrading extracellular and membrane-associated therapeutic targets.
- To identify translational barriers and future opportunities for next-generation drug discovery and clinical development.

2. Scientific Foundations of Lysosome-Targeting Chimeras

2.1 Concept and Historical Development of LYTAC Technology

Lysosome-targeting chimeras were born out of the wider trend of moving towards event-driven pharmacology, in which proteins associated with the disease are targeted for destruction rather than simply short-term inhibition. The early LYTAC designs were made up of two components: a target-binding ligand and a moiety that could be recognized by endogenous lysosome-trafficking receptors, and thus facilitate the internalization of extracellular and membrane proteins. The technology has since been developed through successive platforms, which contained endocytic signaling motifs, chemically defined receptor ligands and mechanisms for spatiotemporal control, going beyond the initial glycopolypeptide constructs (Fang et al., 2024). Such developments made LYTACs flexible degraders more relevant to precision therapeutics (Liang et al., 2026).

2.2 Differences Between Protein Inhibition and Targeted Degradation

Conventional inhibitors usually rely on binding to an active site or an allosteric site and usually inhibit a single function of a multidomain protein. By targeted degradation the entire protein is destroyed, which can include catalytic, scaffolding and signaling functions. LYTACs take this a step further, allowing for endocytosis and lysosomal delivery of cell surface and extracellular targets. This means that their efficacy does not rely exclusively on the inhibition but also on productive trafficking, which is possible without any requirement for binding of a drug to the conventional binding pocket (Zhang et al., 2025). However, the selectivity, receptor availability, internalization kinetics and lysosomal processing are all critical for the pharmacological performance.

2.3 Position of LYTACs Within Targeted Protein Degradation

The LYTACs are used in targeted protein degradation to work in conjunction with the proteasome and autophagy. PROTACs and molecular glues use E3 ubiquitin ligases, while antibody-based PROTACs use antibody recognition to enhance target specificity. AUTACs, ATTECs and

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AUTOTACs guide proteins or damaged organelles to autophagic degradation. Endosome- and lysosome-targeting platforms, on the other hand, are responsible for the degradation of extracellular or membrane-associated proteins via endosomal and lysosomal pathways (Shen et al., 2025). LYTACs are therefore unique in their ability to interact with the non-cytosolic proteome, as well as their reliance on the lysosome-trafficking receptors (Wang et al., 2026), providing ample opportunities for precision oncology (Table 1) (Figure 1).

Table 1. Comparison of LYTACs with major targeted protein-degradation platforms

Platform	Degradation route	Principal target space	Distinguishing feature	References
PROTACs and molecular glues	Ubiquitin–proteasome	Intracellular proteins	Recruitment of E3 ubiquitin ligases	(Wang, Tang, & Li, 2026)
Antibody-based PROTACs	Antibody-guided proteasome pathway	Antigen-defined targets	Antibody recognition combined with proteasomal degradation	(Liang et al., 2026)
AUTACs, ATTECs and AUTOTACs	Autophagy–lysosome	Proteins, aggregates and organelles	Autophagic sequestration and clearance	(Shen et al., 2025)
LYTACs	Receptor-mediated endolysosomal pathway	Extracellular and membrane proteins	Target–shuttling-receptor bridging	(Fang et al., 2024)
Engineered endocytic platforms	Enhanced lysosomal accumulation	Cell-surface receptors	Endocytic motifs or molecularly built ligands	(Zhang et al., 2025)

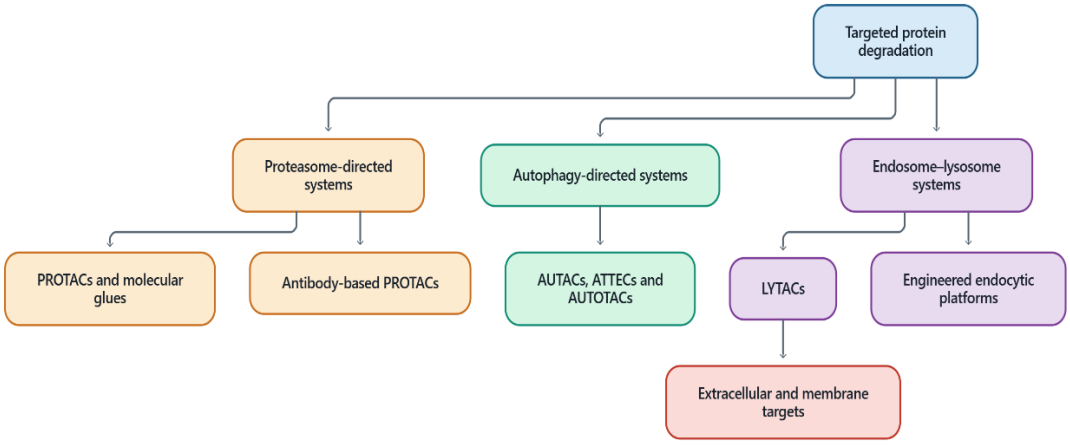

Figure 1. Position of LYTACs within targeted protein degradation

3. Molecular Mechanisms of LYTAC-Mediated Protein Degradation

3.1 Recognition of Extracellular and Membrane-Associated Targets

The degradation process starts with the selective recognition of an accessible epitope on an extracellular or transmembrane protein by LYTAC, which initiates the process. The process is initiated by the selective recognition of an accessible epitope on an extracellular or transmembrane

protein by LYTAC. This recognition can be provided by antibodies, peptides, aptamers or small molecule ligands, depending on the target structure and the nature of the therapeutics. Binding has to be sufficiently stable to the cell surface to allow for efficient ternary complex formation but not prevent further dissociation inside the cell. GLP-1-derived LYTACs are a proof of concept example of how a biologically active peptide can be modified to target specific extracellular and membrane proteins and still maintain the capacity for lysosomal degradation (Zhu et al., 2025).

3.2 Recruitment of Lysosome-Shuttling Receptors

The second functional module contains a lysosome-shuttling receptor and a module for connecting the captured target to the endosomal trafficking machinery. The receptors that are exploited are the sortilin, asialoglycoprotein receptor, cation-independent mannose-6-phosphate receptor and other tissue-enriched internalizing receptors. CI-M6PR binds glycan with Mannose-6-phosphate that directs transport to endolysosomal compartments, which sets a precedent for receptor-directed delivery (Seo and Oh, 2022). The binding affinity and valency of the ligand influences the therapeutic safety, internalization capacity, receptor selection, the biodistribution of the receptor and cell specificity; thus, the affinity of the ligand must be optimized without the risk of receptor saturation or surface retention in the absence of internalization.

3.3 Receptor-Mediated Endocytosis and Intracellular Trafficking

Ternary complex formation leads to receptor clustering which results in invagination of plasma membrane and internalization via clathrin-dependent or alternative endocytic pathway. Newly generated vesicles bring the receptor–LYTAC–target complex to early endosomes, where the continued acidification and movement of the ER–LYTAC–target complex is regulated by trafficking mechanisms to influence where the target will go inside the cell. Here, the authors show that membrane proteins can be removed rapidly and continually with alternative shuttling receptors, mRNA-encoded LYTAC systems (Chang et al., 2025). Uptake rates depend on the number of receptors, the mobility of the receptor, its complex geometry, the valency of the ligand, and the quantity of endocytic machinery available in the cell.

3.4 Endosomal Sorting and Lysosomal Degradation

The internalized complex is sorted by changing binding interactions in the lumen of early and late endosomes in response to changes in luminal pH. Proteins that remain in maturing vesicles are then transported to lysosomes where they are broken down into peptides and amino acids by the acidic hydrolases (Alhowyan & Harisa, 2025). Rapid endosomal recycling and non-degradative trafficking pathways must be avoided for productive degradation. The integrity, acidification, protease activity and vesicular fusion of the lysosomes are thus directly related to the pharmacological performance. The inability of the lysosomes to function properly or the accumulation of excessive cargo may lead to variable or toxic treatments.

3.5 Recycling of Lysosomal Receptors

After binding to cargo, the receptors are transported to the lysosomes and then most of them are directed back to the plasma membrane or to the appropriate intracellular compartment by lysosome-shuttling receptors. Recycling keeps receptors free so that rounds of target capture can be repeated, thus maintaining the event-driven nature of LYTAC pharmacology. Non-covalent Fc–IGF2 complex Fc-LYTACs take advantage of the CI-M6PR trafficking mechanisms while separating the target recognition from the receptor recruitment (Yoda et al., 2026). The efficiency of recycling is receptor dependent, ligand dissociation, endosomal pH, sorting motifs, and construct avidity; ligand binding may alternatively lead to degradation.

3.6 Biological Determinants of Degradation Efficiency

The efficiency of LYTAC is determined by: target biology, construct design, receptor distribution,

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and cellular trafficking. Factors that are important are epitope accessibility, target density, receptor abundance, internalization rate, ternary-complex cooperativity, linker length, molecular size, ligand valency, endosomal sorting, and lysosomal capacity (Zhang et al., 2026). The size and persistence of depletion in vivo is further influenced by the activity of tissue penetration, proteolytic stability, pharmacokinetics and target resynthesis. Multibody enabled lysosome targeting conjugates reveal the potential of modular recognition and combination approaches for expanding target coverage, while increasing the structural complexity may present challenges in delivery and manufacturing (Figure 2).

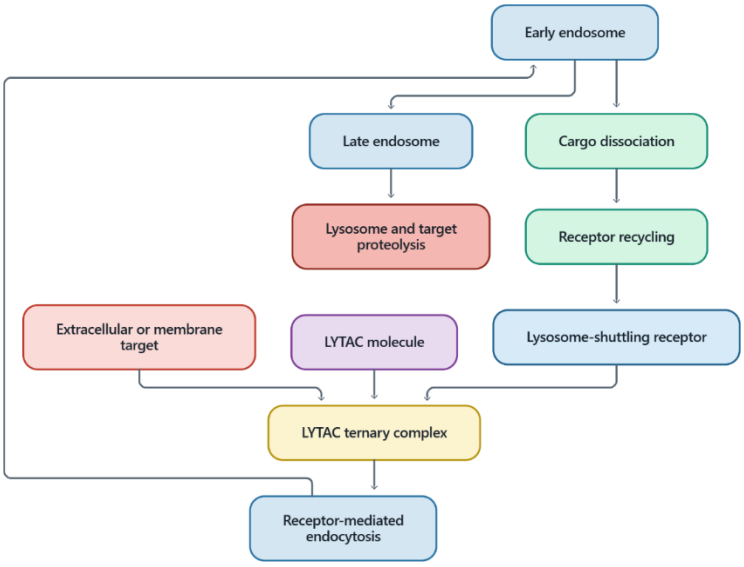

Figure 2. Molecular mechanism of LYTAC-mediated degradation

4. Molecular Architecture and Design Principles

Target engagement, internalization, trafficking, and degradation of a lysosome-targeting chimera is driven by target binding, lysosome recruiting ligand, and the properties of the linker. Binding modules can be whole antibodies, antibody fragments that have high affinity and epitope selectivity, peptides with compact and tunable recognition, aptamers that can be chemically modified and folded into programmable shapes, or small molecule ligands that can be synthesized and will have better tissue penetration. The selection should take into account the route of administration, the molecular size, the internalisation behaviour, the binding to the target and the accessibility of the target, as recognition without efficient internalisation cannot lead to efficient degradation. The larger targeting-chimera field shows that a modular recognition can transform a wide variety of binding ligands into event-driven pharmaceuticals (Hollingsworth et al., 2023). Covalent dual LYTACs are also mediated by aptamers, demonstrating how aptamer-based, irreversible target capture and irreversible protein degradation on the cell surface can be combined (Peng et al., 2026). Lysosome-recruiting module dictates the targetting of the hijacked endocytic receptor and this has a significant impact on tissue selectivity. Mannose-6-Phosphate based ligands are able to bind to the cation-independent mannose-6-phosphate receptors that have relatively ubiquitous expression, while the triantennary N-acetylgalactosamine or tri-GalNAc ligands bind to asialoglycoprotein receptors, for delivery to the liver. Other tissue-specific receptor ligands, which bind integrins, can also induce degradation of other types of cells, if the receptor endosomal sorting and routing to the lysosomes is effective enough (Liu et al., 2026 A). Dual-receptor designs can expand cellular coverage or increase uptake by activating complementary trafficking pathways, but a high valency and complexity of these designs needs to be carefully controlled (Wang et al., 2025). The distance, orientation, flexibility, hydrophilicity and stability of the two functional modules are determined by the linker chemistry. Covalent conjugation ensures structural stability, while non-covalent and supramolecular assembly can facilitate proximity control, modular exchange, or stimulus-responsive properties (Wang et al., 2026). Conjugation to the site is preferred to reduce the product heterogeneity and maintain the

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activity of both the ligands. Increase in avidity and receptor clustering can be achieved by multivalency, but too high an affinity or too close a packing, or inappropriate molecule shape can cause trapping at the membrane, non-productive trafficking or block receptor recycling. The degradation efficiency therefore represents an optimum balance and the abundance of cellular receptors, the internalization machinery and the capacity of the lysosomes are still key factors (Ahn et al., 2023). Pharmacological optimization should also enhance the aqueous solubility, proteolytic and plasma stability, circulation time, tissue penetration, biodistribution and clearance, and decrease aggregation, immunogenicity, off-target uptake, and disruption of normal lysosomal function (Table 2).

Table 2. Principal molecular components and design requirements of LYTACs

Design element	Representative options	Primary design role	Major optimization concern	References
Target-binding module	Antibodies, fragments, peptides, aptamers, small molecules	Selective target recognition	Size, affinity and stability	(Hollingsworth et al., 2023); (Peng et al., 2026)
Receptor-recruiting ligand	M6P, tri-GalNAc, integrin or tissue-selective ligands	Endocytosis and tissue targeting	Receptor heterogeneity and saturation	(Liu et al., 2026 A)
Linker and conjugation	Covalent, non-covalent or supramolecular	Controls spacing and orientation	Cleavage and product heterogeneity	(Wang et al., 2026)
Multivalency and geometry	Monovalent, multivalent or dual-receptor	Improves avidity and receptor clustering	Steric trapping and impaired recycling	(Wang et al., 2025)
Developability	Solubility, stability and pharmacokinetics	Supports systemic exposure	Aggregation, clearance and variable uptake	(Ahn et al., 2023)

5. LYTAC Discovery and Development Strategies

The process of discovering LYTAC should start with careful selection of a disease-related extracellular or membrane protein whose elimination should show a significant therapeutic effect. Candidate validation should include proof of causal disease involvement, accessible epitopes, differential expression of the target between diseased and healthy tissues, target turnover, functional redundancy, and the effects of full suppression compared to partial suppression. The structural and biological functions, as well as pathological roles, of proteins in the extracellular and membrane spaces can be mapped to identify targets that are not well targeted by conventional inhibitors (Zhao et al., 2026). Disease context is also critical since neurological diseases can impose blood–brain barrier and tissue-delivery limitations (Zheng et al., 2025) while resistant breast cancers demand targets that are able to bypass adaptive signaling and molecular heterogeneity (Wang, et al., 2026). Discovery of receptors must incorporate tissue expression atlases and quantification of receptor abundance, receptor internalization rate, receptor recycling, endosomal routing, and lysosomal delivery, as well as receptor disease association. Exosomes can be genetically engineered to take advantage of cellular uptake and lysosomal trafficking (Wang et al., 2023). Another approach for targeting specific proteins to be degraded is to create engineered lysosome-associated receptors that cannot be found in nature, but which are designed to recognize and deliver specific proteins to degradation (Gao et al., 2026). Optimized target binder, receptor-recruiting ligand and linker are then united in a candidate synthesis that involves reproducible, preferably site-specific, conjugation. In the modular design, bispecific DNA aptamers were designed to bind two different targets: the one recognizing the target and the other recruiting the lysosomes (Hamada et al., 2023). IGF2-fused LYTAC further suggest that

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receptor-binding fusion constructs can also be used to expand the degradation strategies to infection associated targets (Ma et al. 2026 A). Biochemical assays should be performed first to determine the affinity and binding selectivity of the ligand, complexation, serum stability and the competition of the ligand with endogeneous receptor ligands. The dose–response relationship, time-dependent depletion, receptor dependence, cytotoxicity, recovery following withdrawal of treatment and retention of lysosomal function should then be assessed using cell-based screening. Internalization can be quantified by flow cytometry, live-cell or confocal imaging, or colocalization with endosomal and lysosomal markers, while degradation can be quantified by immunoblotting, ELISA, targeted proteomics or fluorescence based. To confirm mechanism it is important to have lysosomal inhibitors, receptor deficient cells, inactive constructs, and non-binding controls. Epitope location, affinity, valency, linker length, linker flexibility, receptor-ligand density, molecular geometry, stability, solubility and the pharmacokinetics of the molecule should be compared in structure–activity and degradation–activity relationships. Poor solubility, permeability, aggregation and systemic exposure are important design issues that can be addressed with formulation principles developed for other chimeric degraders (Maurya et al., 2026). Finally, computational modelling and artificial intelligence can prioritize target–receptor pairs, predict ternary-complex geometry, optimize linkers, estimate developability, and incorporate imaging, omics, and degradation data; but, predictions need to be built on experimentally diverse training sets, be interpretable, and be validated in the lab in a prospective way (Table 3) (Figure 3).

Table 3. Integrated workflow for LYTAC discovery and optimization

Development stage	Core activity	Principal output	References
Target validation	Confirm disease relevance, accessibility and differential expression	Validated degradation target	(Zhao et al., 2026); (Wang, Song, et al., 2026)
Receptor selection	Assess expression, uptake, recycling and tissue distribution	Suitable shuttling receptor	(Gao et al., 2026)
Candidate construction	Combine binder, linker and receptor ligand	Chemically defined candidates	(Hamada et al., 2023); (T. Wang et al., 2023)
Biochemical screening	Measure affinity, complex formation and stability	Active binding constructs	(Ma et al., 2026 A)
Cellular screening	Quantify uptake, degradation and receptor dependence	Mechanistically validated hits	(Gao et al., 2026)
SAR and DAR analysis	Optimize linker, valency, affinity and formulation	Developable lead candidate	(Maurya et al., 2026)
Computational design	Apply docking, modelling and developability prediction	Prioritized candidates for validation	(Zheng et al., 2025)

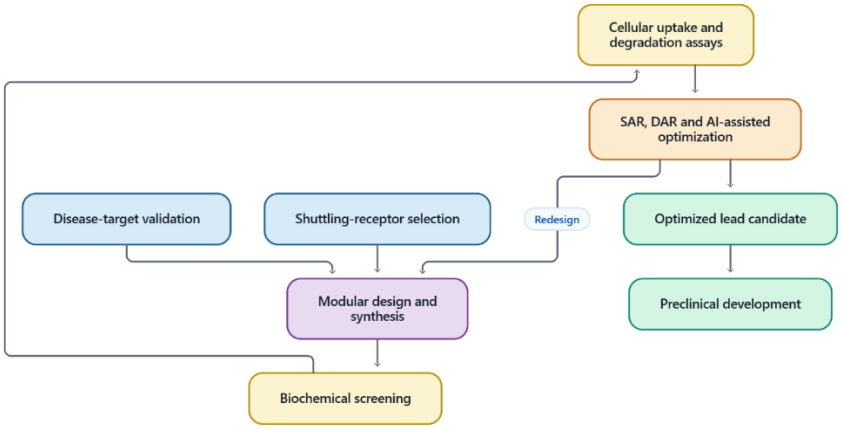

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Figure 3. LYTAC discovery and development workflow

6. Therapeutic Applications and Emerging Disease Targets

LYTACs are broadly therapeutic, due to their ability to target cell surface and extracellular proteins that are not easily targeted by conventional occupancy-based drugs (Ma et al., 2026 B). The epidermal growth factor receptor and human epidermal growth factor receptor 2 are prominent candidates in cancer due to their complete removal potentially impacting catalytic signaling, scaffolding mechanisms, receptor recycling, and compensatory reactivation. Other immune-checkpoint proteins such as programmed death-ligand 1 (PD-L1; CD274) and CD47 are also promising targets for reinvigorating antitumour immunity. These proteins can be converted to programmable degradation substrates through antibody and antibody fragments making highly selective recognition modules (Chen & Hu, 2026). While the antibody–drug conjugates aim to trigger the delivery of cytotoxic payloads, the antibody-based degraders aim to the elimination of the bound target by the endogenous trafficking machinery (Garcia-Barrantes & Junutula, 2026). In addition, targeted chimeras can be developed based on nanoparticles to further enhance tumour accumulation, protect complex constructs and control multivalent uptake (Liu et al., 2026 B). In addition to oncology, LYTACs could clear pro-inflammatory cytokines and pathogenic autoantibodies and membrane receptors that sustain inflammatory or autoimmune signaling. Tissue-specific shuttling receptors can mediate the degradation of profibrotic receptors, as well as extracellular-matrix regulators, circulating metabolic mediators or hepatocyte-associated targets for fibrotic and metabolic applications. This kind of expansion is part of a larger trend of drug discovery being aimed at proteins previously thought to be untargetable by drug. Neurological applications are more difficult due to limited access to the brain, but there are conceptually relevant targets for extracellular protein aggregates, toxic oligomers, and disease-associated neuronal surface proteins. The autophagy-directed strategies provide complementary methods for intracellular aggregates and damaged organelles that cannot be targeted with the conventional LYTACs (Kocak et al., 2022). For infectious diseases, the degraders can be targeted to pathogen-associated surface antigens, viral envelope proteins, infected-cell markers, or secreted toxins, but the accessibility of the target and its trafficking in different species needs to be well validated. Another class of proteins of interest, which can be captured by LYTACs and targeted for lysosomal destruction, are soluble extracellular proteins such as cytokines, growth factors, toxins, pathological antibodies, etc (Liszewski, 2026). The acidic nature of the lysosome and the various hydrolases present inside it creates a potent biochemical compartment to process the internalized therapeutic cargo (Dharmasivam & Kaya, 2025). In combination with disease-specific therapeutic strategies for protein stabilization, which include DUBTACs (Ma et al., 2025), the ability to remove excess toxic proteins by LYTAC may eventually be combined with protein protection in an overall strategy for treating such diseases. In general, next generation degraders could allow the transition from temporary functional blockade to selective control of the abundance of disease associated proteins (Whyte, 2024) (Table 4) (Figure 4).

Table 4. Emerging therapeutic applications of LYTAC platforms

Disease area	Representative targets	Therapeutic rationale	Principal barrier	References
Cancer	EGFR, HER2, PD-L1 and CD47	Remove oncogenic and immune-checkpoint proteins	Tumour-selective delivery	(Chen & Hu, 2026)
Inflammatory and autoimmune disorders	Cytokines, autoantibodies and immune receptors	Suppress persistent immune signaling	Systemic immune effects	(Whyte, 2024)
Fibrotic and metabolic	Profibrotic receptors and	Interrupt pathogenic extracellular	Tissue and receptor	(Liszewski, 2026)

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diseases	metabolic mediators	signaling	heterogeneity	
Neurological disorders	Extracellular aggregates and neuronal receptors	Clear aggregation-associated proteins	Blood–brain barrier	(Kocak et al., 2022)
Infectious diseases	Viral proteins, pathogen antigens and toxins	Remove pathogen-associated targets	Species-specific trafficking	(Dharmasivam & Kaya, 2025)
Soluble protein disorders	Cytokines, growth factors and pathological antibodies	Capture and degrade circulating proteins	Exposure and receptor capacity	(Liu et al., 2026 B)

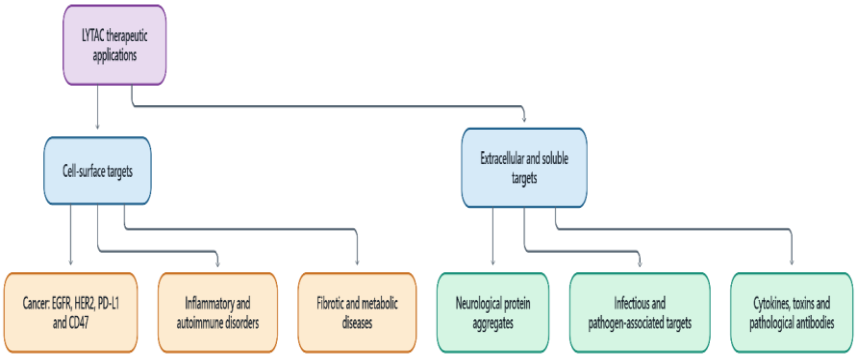

Figure 4. Therapeutic target space of LYTAC platforms

7. Preclinical and Pharmaceutical Development

7.1 In Vitro Degradation Potency and Selectivity

Concentration and time dependent degradation, maximum degradation, half-maximal degradation concentration, recovery kinetics and selectivity against related proteins should be determined first as part of the preclinical assessment. Binding alone is not enough because productive formation of a ternary complex, binding to an internaliser, and routing to the lysosomes are all necessary to obtain the activity. The degradation performance of a HER2-directed bispecific aptamer LYTAC is significantly dependent on the molecular spacing of the LYTACs as shown in length studies (Yoda et al., 2025). Conventional EGFR inhibitors and proteasome-directed EGFR degraders can be used orthogonal to examine if targeting the lysosomes offers unique advantages in terms of target coverage, persistence or resistance (Li et al., 2023).

7.2 Cellular Uptake and Tissue Specificity

Cellular internalization should be measured in both target-positive and target-negative cells, as well as receptor-deficient cells to elucidate specific endocytosis from non-specific adsorption. The uptake is measured in population-level by flow cytometry, while confocal imaging and organelle colocalization allow to visualize the progression through the early endosomes, late endosomes and lysosomes (Li et al., 2026). Comparisons of receptor expression in relevant tissues and disease models are important since the expression in one cell-line may not be representative of more extensive expression. Engineered nanovesicles are used to show coordination of cellular entry with cancer selective immunotherapeutic responses by tuning the composition of nanovesicles and receptor engagement (Xiao et al., 2026).

7.3 Pharmacokinetics and Biodistribution

Validated assays of intact LYTAC, free target-binding component, receptor ligand and degradation products are necessary for pharmacokinetic development. After single and repeated dosing, plasma

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stability, exposure, clearance, tissue penetration, target occupancy and duration of depletion should be measured. Biodistribution studies should make a distinction between desired uptake and accumulation in liver, spleen, kidney or phagocytic cells. Targeted degraders have a wide variety of sizes and molecular structures, and their pharmacodynamics are not predictable by traditional small molecule studies only and must be evaluated throughout their development (Xue et al., 2023).

7.4 In Vivo Therapeutic Efficacy

Efficacy should be shown in vivo and the target should be depleted in diseased tissue, while obtaining a pharmacologically significant response. The endpoints can be: regression of tumour, delay of tumour development, activation of immunity, reduction of inflammatory signaling or clearance of pathological extracellular proteins. Dose–response and time course experiments should be correlated with systemic exposure and tissue uptake, degradation, pathway modulation, and therapeutic response. The covalent peptide-based lysosome-targeting platforms for cancer immunotherapy demonstrate the stability of target capture to be translated into antitumour activity, highlighting the importance of receptor dependent and non-targeting controls (Xiao et al., 2025).

7.5 Toxicity, Immunogenicity, and Off-Target Effects

On-target toxicity in normal tissues, unintended degradation of related proteins, cytokine release, complement activation, lysosomal stress and changes in receptor homeostasis should be evaluated for safety. Constructs containing antibodies also need to be evaluated for immunogenicity, Fc mediated effects, aggregation and anti-drug antibodies. Monitoring clinical chemistry, haematology, organ pathology, immune responses and recovery following the end of treatment is recommended for repeat-dose studies. New antibody-mediated degradation strategies underscore the importance of targeting specific regions of the antigen and recruiting receptors to specific tissues for highly selective degradation, while not sacrificing efficient elimination of membrane or extracellular targets (Wei et al., 2025).

7.6 Formulation and Drug-Delivery Approaches

Formulation should maintain structural integrity, binding activity, solubility and stability during storage, administration and systemic circulation. In some cases, buffered solutions, lyophilization, polymeric carriers, lipid nanoparticles, nanovesicles or local delivery systems can be of use, depending on the molecular format. The properties to be controlled by carrier selection are particle size, surface charge, release kinetics, tissue penetration, uptake, but not degradation or clearance by the immune system. Nanovesicle-based lysosome targeting platforms are promising delivery platforms as targeting, protection, and multivalent receptor engagement can be achieved in a single engineered nanovesicle (Xiao et al., 2026).

7.7 Manufacturing, Scalability, and Quality Control

Translation demands that the production processes can be reproduced and the identity, purity, conjugation site, distribution of linkers, density of ligands, aggregation, residual reagents and biological potency can be controlled. Molecular, binding to both target and shuttling receptor, internalization capacity, degradation activity, sterility and stability should be part of analytical release testing. Modular click chemistry platforms can help streamline the LYTAC assembly process and enable the quick switching out of target-binding or receptor-recruiting components (Szijj et al., 2026). However, scale up needs to be accompanied by validated reaction conditions, batch comparability, reference standards, storage requirements and quality attributes directly associated to clinical performance (Table 5) (Figure 5).

Table 5. Preclinical and pharmaceutical evaluation framework for LYTACs

Development domain	Core measurements	Advancement criterion	References

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Potency and selectivity	DC50, Dmax, time course, recovery and off-target effects	Selective receptor-dependent degradation	(Yoda et al., 2025); (Li et al., 2023)
Uptake and tissue specificity	Flow cytometry, imaging and lysosomal colocalization	Preferential uptake in target tissue	(Xiao et al., 2026)
Pharmacokinetics	Exposure, half-life, clearance and organ distribution	Sustained tissue exposure	(Xue et al., 2023)
In vivo efficacy	Tissue degradation and therapeutic response	Exposure–degradation–response relationship	(Xiao et al., 2025)
Safety	Immunogenicity, cytokines, lysosomal stress and organ toxicity	Acceptable reversible toxicity	(Wei et al., 2025)
Formulation	Stability, solubility, particle size and release	Preserved activity during delivery	(Xiao et al., 2026)
Manufacturing	Identity, purity, conjugation, ligand density and potency	Reproducible batch quality	(Szijj et al., 2026)

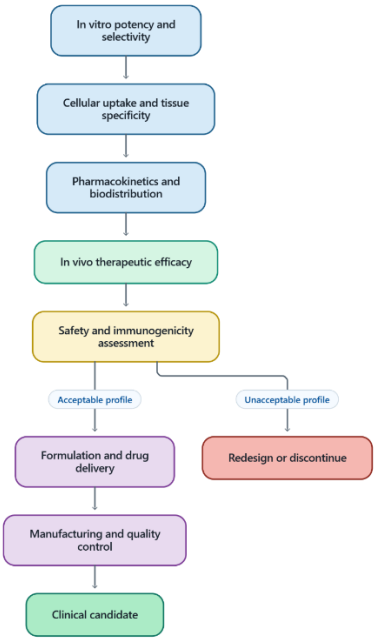

Figure 5. Preclinical-to-pharmaceutical development pathway

8. Translational Challenges, Research Gaps and Future Directions

Biological heterogeneity, lack of understanding of mechanisms and modality-dependent pharmaceutical limitations continue to restrict clinical translation of LYTACs. Lysosome-shuttling receptors are not readily present in all tissues, tumours or patients and the expression of these receptors can be dynamic with disease progression and previous treatment. Other poorly understood mechanisms such as endosomal sorting, receptor recycling, dissociation of cargo and delivery to the lysosome also makes it difficult to predict degradation from binding affinity alone. Therefore, the construct activity measured on different targets and/or cell types can vary significantly due to differences in epitope accessibility, membrane mobility, internalization capacity, target resynthesis and lysosomal competence. LYTACs are also often large and/or multivalent, thus having poor tissue penetration, high clearance rate, low bioavailability, proteolytic instability, or hepatic and splenic accumulation. The issues of immunogenicity, anti-drug antibodies, lysosomal stress, receptor disruption, and delayed toxicity are of concern with repeated administration and will need to be evaluated over the long-term in physiologically relevant models. Lack of standardized assays and reporting criteria for internalization, maximum degradation, degradation potency, selectivity,

recovery kinetics and receptor dependence are also obstacles to progress. Target abundance, expression of shuttling-receptors, endocytic activity, lysosomal function, and disease-specific tissue accessibility should therefore be included in the development of biomarkers to aid in patient selection and in optimizing the dose. Tissue selective receptor ligands, dual receptor recruitment, conditionally activated binders, cleavable linkers, and externally-controlled and microenvironment-controlled degradation should all be highlighted for next generation platforms. LYTACs are not necessarily used in combination with other targeted agents; they may be part of a combination therapy with immunotherapy, kinase inhibitors, or antibodies, which may enhance responses and reduce compensatory signaling, but may need to be tested sequentially, with appropriate dose, and with shared toxicity. Acceptable off-target profiles, immunogenicity thresholds, limits of biodistribution and comparability requirements for structurally complex or heterogeneous products must be defined by regulatory strategies. For this to become clinical reality, scalable manufacturing, reproducible conjugation, validated potency assays, robust quality control, relevant animal models, companion diagnostic, and informative PKP-D biomarkers, and carefully planned early phase trials to show target degradation and a meaningful therapeutic response, will all be needed.

9. Conclusion

Lysosome-targeting chimeras are extending the reach of drug discovery by creating a new paradigm in which proteins that are selectively bound are actively removed from the cell. They make a major contribution in selectively degrading targets that are poorly targeted by conventional inhibitors or proteasome-dependent technologies, such as extracellular, soluble, and membrane-associated targets. This ability can be used to target and destroy oncogenic receptors, immune-checkpoint proteins, inflammatory mediators, pathological aggregates, and pathogenic molecules. But therapeutic success isn't only about target affinity. The selection of a lysosome-shuttling receptor, the rational integration of the target-binding and receptor-recruiting domains, the optimization of the geometry of the linker and the control of the molecular valency are crucial to successful internalization and degradation. It is also important that the platform is optimized to express the receptors in the tissue to be targeted to enhance the effectiveness of the platform and reduce the uptake of the platform by healthy organs. Standardized preclinical assays are needed to quantify internalization, degradation potency, maximum target depletion, selectivity, recovery kinetics, receptor dependence, and lysosomal involvement that will help advance progress toward clinical application. These measurements should be combined with pharmacokinetic, biodistribution, immunogenicity and long-term safety assessments to provide a solid exposure–degradation–response relationship. Potential developments beyond current capabilities include compact ligations, programmable activation of the molecule, tissue-specific receptors, optimized delivery systems, and scalable manufacture. Optimized LYTACs could be an effective therapy for converting many inaccessible proteins into drug targets that can be used clinically with rigorous validation and patient selection based on biomarkers.

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