



From Small Molecules to Supramolecular Assemblies: The Paradigm Shift in Targeted Protein Degradation

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From Small Molecules to Supramolecular Assemblies: The Paradigm Shift in Targeted Protein Degradation

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ABSTRACT

Targeted protein degradation (TPD) offers a promising route to undruggable targets *via* the ubiquitin-proteasome pathway, but small-molecule PROTACs suffer from poor druggability, low tissue selectivity, and laborious linker optimization. Existing reviews cover individual nano--platforms separately; few have systematically compared the four core supramolecular degraders—SupTACs, hexamer-linker Nano-PROTACs, Split-and-Mix systems, and Nano-TACs. This review focuses on the paradigm shift from single small molecules to supramolecular assemblies, comparing design principles, fabrication routes, and therapeutic advantages across degradation pathways, substrate scope (proteins and RNA), and targeting modalities. It highlights the roles of non-covalent assembly, multivalent cooperativity, tissue-targeted delivery, pathway expansion, and modular reconfiguration in overcoming traditional bottlenecks, summarizes the technological evolution of

self-assembled degradation systems, and analyzes current challenges including assembly heterogeneity, *in vivo* controllability, clinical translation, and safety, providing a technical and theoretical framework for next-generation precision-targeted, translatable degraders.

Keywords: Targeted Protein Degradation, Supramolecular Assembly, Peptide Self-assembly, Dual-pathway Degradation, Autophagy Degradation, RiboTAC

INTRODUCTION

Targeted protein degradation overcomes limitations of conventional inhibitors by exploiting endogenous degradation machinery. With over 30 TPD agents in clinical development, the PROTAC vepdegestrant (ARV-471) received FDA approval in May 2026 as the first-in-class drug.¹ Nevertheless, canonical small-molecule PROTACs face three core translational barriers: poor permeability, low tissue selectivity, and empirical linker optimization (**Table 1**).

Supramolecular self-assembled degraders have emerged as a promising alternative, with notable pharmacologic advantages: prolonged circulation, intrinsic organ tropism, and multivalent cooperativity that expands access to challenging targets. Prior nanocarrier PROTAC strategies—including polymer-PROTAC conjugates, inorganic gold/silica nanoparticle systems, and conventional liposomal PROTACs—only improve solubility and pharmacokinetics *via* covalent tethering or passive encapsulation, without altering the core degradation machinery or supporting modular rearrangement.

In contrast, the four supramolecular platforms—SupTACs, hexamer-linker Nano-PROTACs, Split-and-Mix SM-PROTAC, Nano-TACs—offer three strengths absent from static nanocarriers: (1) streamlined production *via* spontaneous noncovalent co-assembly;^{2,3} (2) modular interchangeability of target/E3-recruiting units, enabling plug-and-play design;⁴ (3) tissue-selective delivery through diverse targeting mechanisms (**Figure 1A**). We define supramolecular degraders as nanostructures where reversible noncovalent forces directly govern both particle formation and ternary complex-mediated degradation; auxiliary liposomal variants

such as LipoSM-PROTAC are classified as delivery-enhanced derivatives of the core SM-PROTAC scaffold rather than standalone supramolecular architectures.

These merits establish supramolecular self-assembly as a significant advance over conventional small-molecule PROTACs and static covalent nanocarrier degraders. This paradigm shift moves beyond rigid single-molecule structures toward dynamic, tunable supramolecular assemblies, integrating nanotechnology, chemical biology and stimuli-responsive engineering to advance TPD. Here, we highlight four representative supramolecular nano-degrader platforms that exemplify this paradigm shift: SupTACs, hexamer-linker Nano-PROTACs, SM-PROTACs, and Nano-TACs (**Figure 1**). Unlike earlier reviews of single systems, this work delivers a systematic cross-platform comparison of degradation pathways, target substrates and tissue targeting, alongside platform-specific manufacturing and biosafety barriers (**Figure 1B**).

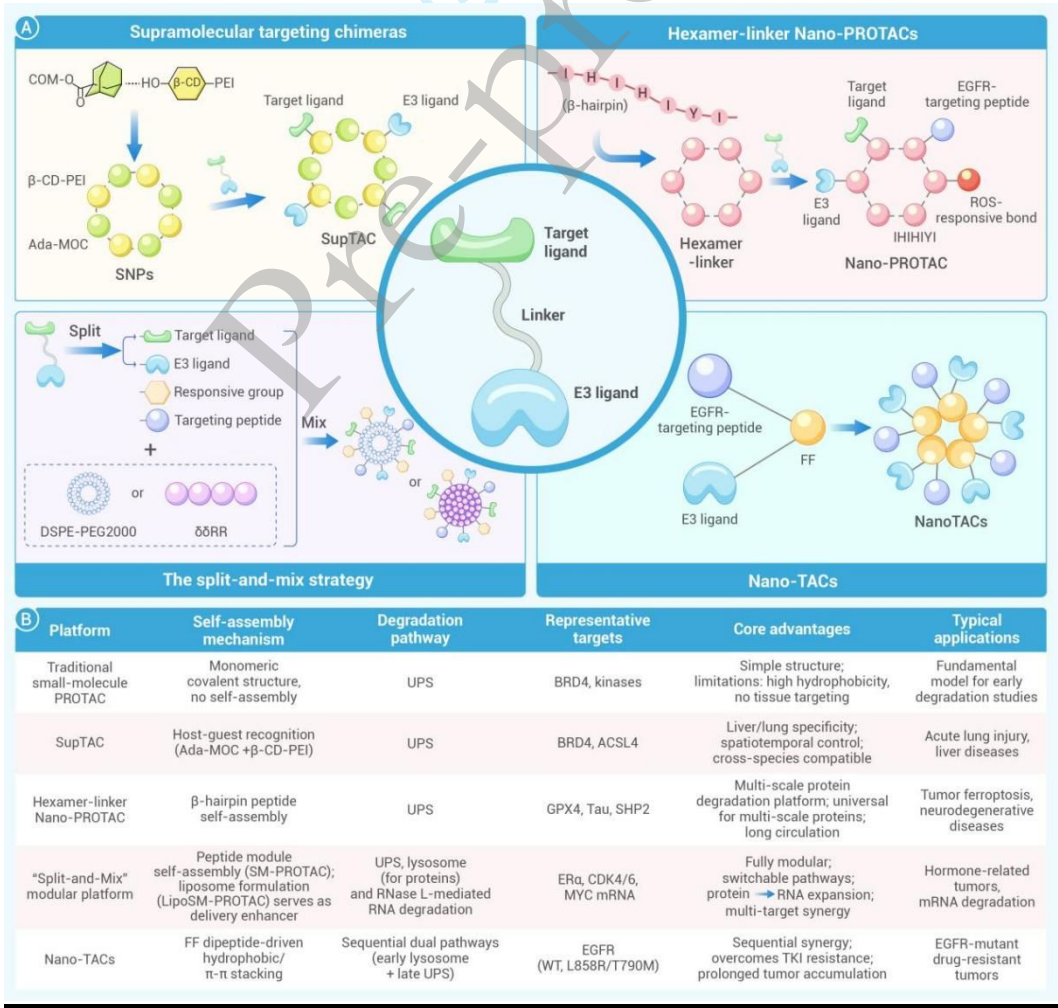


Figure 1. Overview of supramolecular nano-degrader platforms for targeted protein degradation

(A) Schematic illustration of the working mechanisms of four representative supramolecular degraders: SupTACs, hexamer-linker Nano-PROTACs, Split-and-Mix systems, and Nano-TACs. Each platform relies on distinct noncovalent intermolecular forces to assemble functional nanostructures for targeted protein degradation. (B) Comparative summary of the self-assembly mechanism, degradation pathway, representative targets, core advantages, and typical applications of traditional small-molecule PROTACs and the four supramolecular platforms shown in (A).

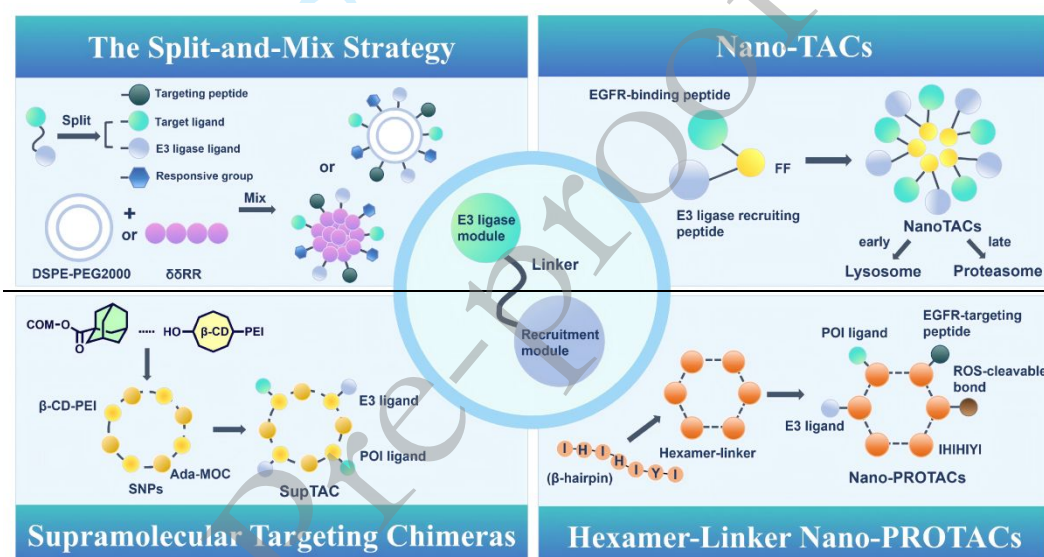


Figure 错误！未指定顺序。1 Schematic illustration of four supramolecular nano-degrader platforms for targeted protein degradation.

1. Supramolecular Targeting Chimeras (SupTACs): Spatiotemporally Resolved *In Vivo* Protein Degradation

SUPRAMOLECULAR TARGETING CHIMERAS (SUPTACS): SPATIOTEMPORALLY RESOLVED *IN VIVO* PROTEIN DEGRADATION

Liu et al. reported SupTACs, which leverage host-guest recognition (noncovalent host-guest interaction) to drive self-assembly and co-localize target

protein ligands and E3 recruiters on nanoparticle surfaces, enabling tissue-selective and temporally controlled protein degradation *in vivo*. The system comprises adamantane-functionalized metal–organic cages (Ada-MOC) and β -cyclodextrin-modified polyethylenimine (β -CD-PEI); tuning the component ratio engineers surface charge and organ-specific biodistribution.

In female BALB/c mice, SupTAC-Liver (β -CD-PEI:Ada-MOC = 6:1) preferentially accumulated in the liver with $80.2\pm5.3\%$ BRD4 degradation at 24 h, while SupTAC-Lung (10:1) achieved $61.4\pm4.7\%$ lung-specific degradation.² Lung targeting relies on vitronectin adsorption and integrin $\alpha\beta3$ interaction, whereas liver targeting depends on apolipoprotein E (ApoE)-mediated recognition of the low-density lipoprotein receptor (LDLR), validated by LDLR-knockout mice and protein corona mass spectrometry.

SupTACs showed translational potential: lung-specific BRD4/MEK degradation was achieved in rabbits and rhesus monkeys with no off-target effects, and azide-caged SupTACs enabled precise temporal control *via* bioorthogonal Staudinger reduction. In acute lung injury models, lung-targeted ACSL4 degradation reduced lipid peroxides by 62.3% with marked histopathological improvement.

By integrating nanoparticle surface engineering with endogenous receptor–ligand systems, SupTACs resolve the tissue-specificity and temporal-control bottlenecks of TPD.

Nevertheless, SupTACs face platform-specific challenges rooted in protein corona-dependent targeting: corona composition is sensitive to physiological variability, with SupTAC-Lung accumulation efficiency dropping from 61% to 38%.² The Ada-MOC: β -CD-PEI ratio (6:1 for liver, 10:1 for lung) demands precise control, as deviations may unpredictably shift biodistribution, and standardized protein corona profiling is essential for batch consistency.

2. Hexamer-Linker Nano-PROTACs: Spatially Adaptive, Multi-Scale Protein—Degradation
HEXAMER-LINKER NANO-PROTACS:
SPATIALLY ADAPTIVE, MULTI-SCALE PROTEIN

DEGRADATION

Zhang et al. reported a β -hairpin peptide-based hexamer-linker Nano-PROTAC: the IHIHIYI heptamer folds into a β -hairpin (folded antiparallel peptide secondary structure) and self-assembles into a β -barrel hexamer (2.9×2.1 nm), enabling spatially adaptive degradation across a broad molecular-weight range and extending plasma circulation half-life from 1.2 h to 27.7 h.³

Conjugating GPX4/Tau ligands and a VHL recruiter to this scaffold yielded a broad-spectrum platform. In EJ-1 cells, Nano-PROTAC_{GPX4} achieved $83.2 \pm 4.1\%$ GPX4 degradation versus $27.3 \pm 3.5\%$ for a linear PROTAC, and in SH-SY5Y cells improved Tau/SHP2 degradation by 58%–63%. Multivalent hexamer interactions stabilize the ternary complex, enhancing degradation efficiency.

A ROS-responsive prodrug version (pNano-PROTAC_{GPX4}) with an EGFR-targeting peptide and dithioacetal linker enabled tumor-specific activation. EGFR-high EJ-1 cells showed ~4-fold higher uptake than EGFR-low HUVECs, and under 50 μM H_2O_2 , GPX4 degradation reached 94% versus 35% without the hexameric linker. In EJ-1 xenografts, pNano-PROTAC_{GPX4} (20 mg/kg) shrank tumors from 1851 to 415 mm^3 with 92% GPX4 degradation and ferroptosis induction.

This strategy eliminates target-specific linker optimization, providing a universal multi-scale degradation platform. However, translation hinges on β -barrel assembly homogeneity, as off-pathway aggregation would compromise multivalent cooperativity, and the prolonged circulation half-life (27.7 h) may amplify the *in vivo* consequences of even minor structural heterogeneity. Furthermore, different ligand conjugations (GPX4, Tau, SHP2) may differentially affect assembly propensity, so case-by-case optimization and real-time monitoring *via* CD spectroscopy and size-exclusion chromatography are warranted.

~~3. The Split-and-Mix Strategy: Generalized Applications from Proteasome to Lysosome and from Proteins to RNA~~ THE SPLIT-AND-MIX STRATEGY: GENERALIZED APPLICATIONS

FROM PROTEASOME TO LYSOSOME AND FROM PROTEINS TO RNA

3.1 Peptide Self-Assembly Platform (SM-PROTAC): A Modular Design Concept
Peptide self-assembly platform (SM-PROTAC): a modular design concept

Yang et al. proposed the “split-and-mix” strategy, dividing the degradation system into independent, interchangeable units that form functional SM-PROTACs *via* non-covalent co-assembly, avoiding complex covalent synthesis and linker optimization.⁴ Using self-assembled diphenylglycine dipeptide ($\delta\delta$) nanospheres as scaffolds, target and E3 ligands were conjugated onto $\delta\delta$ RR (θ) tetrapeptide modules and functional SM-PROTACs formed by simply mixing.

In MCF7 cells, VHL+TMXF- $\theta\theta$ (1:1) induced dose- and time-dependent ER α degradation blocked by MG-132 and MLN7243, confirming dependence on the ubiquitin–proteasome system (UPS), adjusting the VHL:TMXF ratio from 1:3 to 1:5 reduced the DC₅₀ from 100 μ M to 40 μ M. This platform broadly degrades CDK4/6, BRD2/4, MEK1/2, BCR-ABL, AR, EGFR.

The “split-and-mix” strategy enables plug-and-play construction without covalent synthesis, with three expansions: pathway (UPS to lysosomal), substrate (proteins to RNA) and functionality (single- to dual-target/dual-E3).

3.2 Liposome-Enhanced Platform (LipoSM-PROTAC): Two Orders of Magnitude Improvement in Potency
Liposome-enhanced platform (LipoSM-PROTAC): two orders of magnitude improvement in potency

Song et al. constructed liposomal LipoSM-PROTAC, packaging peptide modules into liposomal nanocarriers—an assembly-enhanced delivery strategy rather than a genuine supramolecular assembly. Conjugating VHL and target ligands to DSPE-PEG2000 with folate targeting achieved nearly complete ER α degradation at 2 μ M (~100-fold more potent than the peptide assembly) and inhibited tumor growth by 60–70% in A375 xenograft mice without obvious toxicity.^{5,6}

3.3 Lysosomal Pathway Expansion (SM-CMAD): Broadening Degradable

TargetsLysosomal pathway expansion (SM-CMAD): broadening degradable targets

Wang et al. expanded this strategy to the lysosomal pathway by replacing E3 ligands with the KFERQ chaperone-mediated autophagy motif (SM-CMAD): degradation was blocked by hydroxychloroquine but not by MG-132, and the system effectively degraded ER α , AR, MEK1/2, and BCR-ABL, breaking the limitation that PROTACs act only on intracellular proteins.⁷

3.4 RNA Targeting Expansion (LipoSM-RiboTAC): From Protein to Nucleic Acid RegulationRNA targeting expansion (LipoSM-RiboTAC): from protein to nucleic acid regulation

Jiao et al. extended the platform to RNA by developing LipoSM-RiboTAC, co-assembling RNA-binding modules and RNase L (an endoribonuclease) recruiters into liposomes, achieving RNAi-independent degradation of MYC mRNA (EC₅₀ = 2.99 μ M), JUN mRNA (~50%), and pre-miR-155 (50–60%), abolished by RNase L knockdown.⁸ In xenografts, LipoSM-RiboTAC inhibited tumor growth without organ damage, showing favorable biosafety and low off-target effects.

3.5 Multi-Module Synergistic Platform (Multi-SM-PROTAC): Dual-Target and Dual-E3 Synergistic DegradationMulti-module synergistic platform (Multi-SM-PROTAC): dual-target and dual-E3 synergistic degradation

Wang et al. established Multi-SM-PROTAC: three-module co-assembly simultaneously degraded ER α and CDK4 by over 90%, dual-E3 systems further enhanced degradation, and four-module integration reduced the DC₅₀ to 7.8–10.8 μ M, enabling synergy against tumor heterogeneity and drug resistance.⁹

Collectively, this strategy allows flexible pathway switching, expands substrates from proteins to RNA and supports multi-target synergy, reshaping the degrader paradigm.

Despite these advantages, this plug-and-play design creates quality control hurdles: optimal ligand stoichiometry differs sharply across targets: tuning the VHL–target ratio from 1:3 to 1:5 reduces DC₅₀ from 100 μ M to 40 μ M, highlighting the need for systematic ratio screening. Four-component systems exponentially increase

assembly intermediates, further complicating batch uniformity and requiring high-throughput screening.

**4. ~~Nano-TACs: Overcoming EGFR Inhibitor Resistance~~
NANO-TACS: OVERCOMING EGFR INHIBITOR RESISTANCE**

Jeong et al. developed Nano-TACs by fusing an EGFR-targeting peptide (EHGAMEI), a diphenylalanine self-assembly linker (FF), and a VHL-recruiting peptide (ALAPYIP). Through hydrophobic and π - π stacking (aromatic intermolecular noncovalent force) interactions, these peptides self-assemble into ~144 nm nanoparticles,¹⁰ with MD simulations and DLS screening confirming FF as the essential linker.

Nano-TACs engage sequential dual-pathway degradation: early lysosomal degradation of membrane EGFR (1–3 h), followed by late proteasomal degradation of cytosolic EGFR (6–9 h). This avoids cetuximab’s rebound—at 72 h, cetuximab-treated EGFR rebounded to 66.9%, while Nano-TACs kept EGFR at 6.3%.¹⁰ In TKI-resistant H1975 cells, 1 μ M Nano-TACs degraded mutant EGFR by 82.7%, whereas erlotinib inhibited pEGFR by only 5%.

In CT26 colon cancer xenografts, Nano-TACs (10 mg/kg) reduced tumor volume from 1963 mm³ to 458 mm³ with 96.2% EGFR degradation and 2.8-fold higher apoptosis than cetuximab; in H1975 xenografts, they shrank tumors from 1685 mm³ to 581 mm³, while erlotinib showed no effect (1809 mm³). Nano-TACs exhibited no organ toxicity, in contrast to erlotinib-induced hepatotoxicity and cardiotoxicity.¹⁰

By enabling sequential dual-pathway degradation and extracellular targeting, Nano-TACs achieve sustained, rebound-free EGFR degradation, overcome TKI resistance and receptor recycling.

Despite this efficacy, FF peptide-based Nano-TACs have inherent translational limitations: the ordered lysosomal–proteasomal cascade depends on uniform nanoparticles, and batch fluctuations in size (~144 nm), charge or peptide loading would break pathway coordination. Moreover, FF-mediated hydrophobic/ π - π

stacking is less predictable than host-guest or hydrogen-bond systems, and uneven assembly risks extended off-target exposure. Standard multi-index characterization of size, surface properties and peptide loading is required for clinical translation.

Table 1 Comparison of representative supramolecular degradation platforms and traditional PROTACs.

Platform	Self-assembly mechanism	Degradation pathway	Representative targets	Core advantages	Typical applications
Traditional small-molecule PROTAC	Monomeric covalent structure, no self-assembly	UPS	BRD4, kinases	Simple structure; high hydrophobicity, no tissue targeting	Fundamental model for early degradation studies
SupTAC	Host-guest recognition (Ada-MOC+ β -CD-PEI)	UPS	BRD4, ACSL4	Liver/lung specificity; spatiotemporal control; cross-species compatible	Acute lung injury, liver diseases
β -Hexa-Nano-PROTAC	β -hairpin peptide self-assembly	UPS	GPX4, Tau, SHP2	multi-scale protein degradation platform; universal for multi-scale	Tumor ferroptosis, neurodegenerative diseases

Platform	Self-assembly-mechanism	Degradation-pathway	Repressantive-targets	Core-advantages	Typical-applications
“Split-and-Mix” modular platform	Peptide-module self-assembly (SM-PROTAC)	UPS, lysosome (for proteins)	ER α , CDK4/6, MYC, mRNA	proteins; long-circulation	Hormone-related tumors, mRNA-degradation
	; liposome formulation (LipoSM-PROTAC) serves as delivery-enhancer	and RNase L-mediate d-RNA-degradation on		Fully-modular; switchable-pathways; protein→RNA-expansion; multi-target-synergy	
Nano-TACs	FF-dipeptide-driven-hydrophobic/ π - π -stacking	Sequential dual-pathways (early-lysosome+late-UPS)	EGFR (WT, L858R/T790M)	Sequential-synergy; overcomes-TKI-resistance; prolonged-tumor-accumulation	EGFR-mutant drug-resistant-tumors

5. Perspectives and Challenges

PERSPECTIVES AND CHALLENGES

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2
3
4 Targeted protein degradation is undergoing a paradigm shift from single
5 molecules to supramolecular systems. Self-assembled platforms replace covalent
6 synthesis with noncovalent assembly, boost potency *via* multivalent interactions,
7 enable tissue-targeted delivery, and expand substrates from proteins to RNA,
8 collectively breaking the permeability, selectivity and linker-optimization bottlenecks
9 of canonical PROTACs.^{2,3,10} While this perspective highlights one representative
10 study per platform, the rapidly expanding landscape suggests that future comparative
11 analyses will benefit from broader dataset integration as additional examples emerge.

12
13 Before examining future directions, a foundational contribution merits
14 recognition. Ma and co-workers reported the first carrier-free self-assembling
15 amphiphilic PROTAC system (PRO NPs), which drives spontaneous aggregation *via*
16 hydrophilic linker modification without exogenous excipients—a single-molecule
17 amphiphilicity strategy distinct from the multi-component supramolecular platforms
18 discussed above.¹¹ HA conjugation further enables CD44-targeted tumor
19 accumulation (76.8% TGI), though its narrow scaffold compatibility and unstable HA
20 modification echo the assembly and controllability bottlenecks outlined below.

21
22 Importantly, the paradigm shift rests on a mechanistic distinction. Covalently
23 functionalized Nano-PROTACs are static constructs whose tissue distribution and
24 degradation activity are predetermined at synthesis—their targeting is locked to a
25 single pre-attached ligand and their activity cannot be switched post-administration in
26 response to biological cues. By contrast, supramolecular assemblies are dynamic
27 systems responding to biological microenvironments through reversible non-covalent
28 interactions—manifested in tissue-selective protein corona formation, temporally
29 controlled assembly/disassembly, and plug-and-play modular reconfiguration. The
30 experimental evidence reviewed here—ApoE-LDLR-mediated liver targeting,
31 bioorthogonally activated degradation and module-ratio-tunable activity—collectively
32 demonstrates spatial precision, temporal resolution and synthetic flexibility
33 inaccessible to covalently fixed Nano-PROTACs.

34
35 Beyond platform-specific challenges, common translational hurdles include
36 unpredictable *in vivo* behavior, limited peptide loading, PEG immunogenicity and
37

multi-target safety risks. Dual-target assemblies produce 30–40% proliferation suppression in normal cells (versus 10–15% for single-target constructs),⁹ while free peptide fragments and polydisperse aggregates may drive off-target lysosomal clearance. Tumor-responsive linkers and targeting peptides could alleviate such toxicity. Additional concerns—long-term organ accumulation of non-biodegradable nanomaterials, metal ion leakage from Ada-MOC cages and immunogenic risks of polypeptide carriers—remain inadequately characterized, as do metabolic clearance profiles.

AI-driven tools will accelerate rational platform design. Machine learning enables high-throughput prediction of β -hairpin folding and self-assembly-competent sequences; computational models quantify host–guest binding affinity for SupTAC formation; and AlphaFold-3 and PROsettaC simulate POI–PROTAC–E3 ternary complexes with high fidelity.

Microfluidic fabrication addresses mass-production heterogeneity: chips generate monodisperse nanostructures with precise control over size, charge and ligand loading, and combined with real-time characterization and AI feedback, achieve standardized batch preparation for clinical translation.

With continued optimization, next-generation self-assembled degraders are expected to achieve clinical breakthroughs in drug-resistant tumors, infectious diseases, neurodegenerative disorders, and autoimmune diseases.

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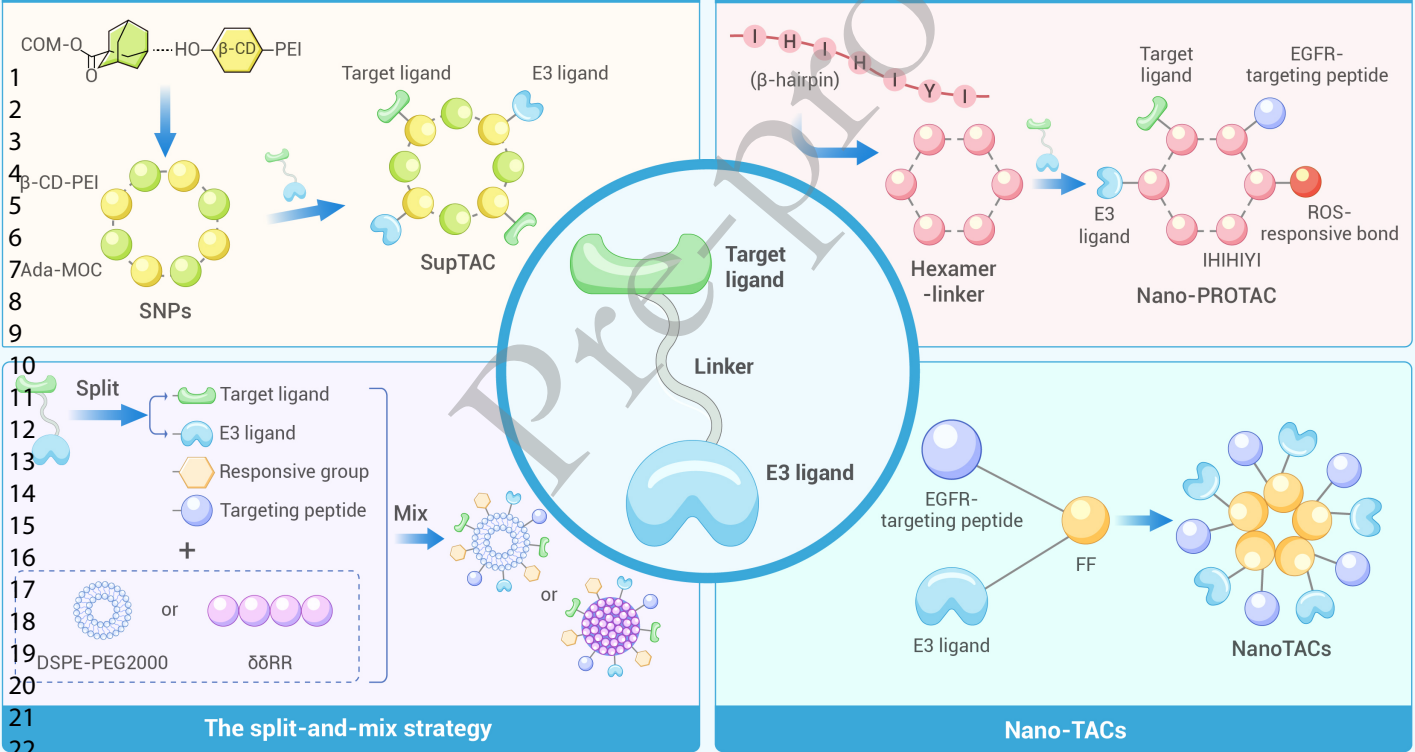
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AUTHOR CONTRIBUTIONS

S.X., P.Z. and J.Y. edited and supervised the manuscript. Q.D. and D.S. wrote the manuscript. All authors contributed to the manuscript and approved the final version.~~All authors contributed to the article and approved the submitted version.~~

DECLARATION OF INTERESTS

Peng Zhan is an Editorial Board member of *The Innovation Drug Discovery* and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.



Platform	Self-assembly mechanism	Degradation pathway	Representative targets	Core advantages	Typical applications
Traditional small-molecule PROTAC	Monomeric covalent structure, no self-assembly	UPS	BRD4, kinases	Simple structure; limitations: high hydrophobicity, no tissue targeting	Fundamental model for early degradation studies
SupTAC	Host-guest recognition (Ada-MOC + β -CD-PEI)	UPS	BRD4, ACSL4	Liver/lung specificity; spatiotemporal control; cross-species compatible	Acute lung injury, liver diseases
Hexamer-linker Nano-PROTAC	β -hairpin peptide self-assembly	UPS	GPX4, Tau, SHP2	Multi-scale protein degradation platform; universal for multi-scale proteins; long circulation	Tumor ferroptosis, neurodegenerative diseases
"Split-and-Mix" modular platform	Peptide module self-assembly (SM-PROTAC); liposome formulation (LipoSM-PROTAC) serves as delivery enhancer	UPS, lysosome (for proteins) and RNase L-mediated RNA degradation	ER α , CDK4/6, MYC mRNA	Fully modular; switchable pathways; protein $\rightarrow$ RNA expansion; multi-target synergy	Hormone-related tumors, mRNA degradation
Nano-TACs	FF dipeptide-driven hydrophobic/ π - π stacking	Sequential dual pathways (early lysosome + late UPS)	EGFR (WT, L858R/T790M)	Sequential synergy; overcomes TKI resistance; prolonged tumor accumulation	EGFR-mutant drug-resistant tumors