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Review

Naturally derived oncolytic peptides: from discovery to clinical translation

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ABSTRACT

Oncolytic peptides have emerged as a distinct class of antitumor agents with the potential to overcome therapeutic resistance and enhance anticancer immunity. Most oncolytic peptides are naturally derived or structurally inspired by natural peptides, and typically display cationic and amphipathic features. Mechanistically, these physicochemical properties enable preferential binding to the negatively charged membranes of cancer cells and subsequent membrane disruption. Beyond direct membrane lysis, many naturally derived oncolytic peptides (NDOPs) perturb intracellular organelle membranes, trigger immunogenic cell death, and modulate immune cells and immune checkpoints, thereby amplifying the cancer-immunity cycle. Through these multifaceted mechanisms, NDOPs show a low tendency to induce drug resistance and can enhance response rates when combined with conventional therapies. Notably, four NDOP-based agents have advanced into clinical trials, underscoring their translational promise. In this review, we summarize the sources, structural features, and mechanisms of NDOPs, highlight innovative therapeutic applications and rational combination strategies, and further discuss the current clinical progress. We also outline key challenges and future directions for the development of NDOPs as next-generation anticancer therapeutics.

1. Introduction

Cancer remains a major global public health burden and a serious threat to human survival [1]. Despite substantial advances in chemotherapy, targeted therapies, and immune checkpoint inhibitors, clinical outcomes for many solid tumors are still limited by intrinsic and acquired resistance. Malignant cells employ diverse mechanisms to evade treatment, including upregulation of drug efflux transporters, on-target mutations, and activation of compensatory signaling pathways, all of which progressively erode therapeutic efficacy [2-4]. Furthermore, extensive tumor heterogeneity, both between patients and between lesions within the same patient and even within a single lesion, makes it difficult for current drugs to eradicate all malignant clones [5]. Ultimately, drug-resistant residual cells drive tumor recurrence and metastasis. These challenges underscore the urgent need for therapeutic modalities with fundamentally distinct mechanisms that can overcome existing treatment barriers.

In recent years, naturally derived oncolytic peptides (NDOPs) have attracted growing interest in both basic research and clinical development [6, 7]. Based on their origin and design strategy, NDOPs can be broadly divided into two categories. The first category comprises peptides directly isolated and purified from natural sources such as animal venoms, amphibian skin secretions, and components of the innate immune system [8, 9]. These molecules are products of evolutionary selection, and their inherent structural motifs often confer strong membrane-lytic activity. The second category, often termed nature-inspired or semi-synthetic oncolytic peptides, includes derivatives generated by rational design on native peptide scaffolds. In this approach, strategic chemical modifications and structural optimization are introduced to tune key features of the peptide backbone, including net charge distribution, amphipathicity, and characteristic secondary structures [10, 11]. These efforts aim to improve proteolytic stability, reduce non-specific cytotoxicity, and enhance antitumor activity. Unlike traditional cytotoxic chemotherapeutics or targeted agents, which typically act on defined intracellular signaling pathways or molecular targets, NDOPs primarily recognize negatively charged components of tumor cell membranes [12, 13]. Their antitumor effects are largely independent of the genetic and epigenetic landscape of malignant cells and instead reflect the unique physicochemical properties of NDOPs. Moreover, many NDOPs engage additional antitumor mechanisms, including lysis of organelle membranes, induction of immunogenic cell death (ICD), modulation of immune checkpoints and immune cells, re-

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programming of tumor cell metabolism, and inhibition of tumor angiogenesis [14-16]. These features markedly reduce the likelihood of resistance and position NDOPs as promising tools in cancer immunotherapy.

Currently, several NDOP-based therapeutics have advanced into clinical trials and have shown encouraging signs of efficacy [17-19]. By combining direct membrane-lytic activity with the capacity to reprogram systemic antitumor immunity, these agents can reduce tumor burden and induce complete responses in patients. This profile underscores their promise as anticancer drugs with mechanisms that are distinct from those of conventional therapies. Therefore, in this review, we comprehensively summarize the sources, structural features, and pharmacological mechanisms of NDOPs, highlight innovative therapeutic applications and rational combination strategies, and discuss outstanding challenges and future directions for this emerging class of peptide-based anticancer agents.

2. Sources and structural features of NDOPs

2.1. Sources of NDOPs

Most NDOPs are produced by biological cells *via* ribosomal synthesis and typically contain 10 to 50 amino acids [20]. Animal venoms, components of the host immune system, and amphibian skin secretions are the three major natural reservoirs for the discovery of NDOPs, representing the most important and promising sources identified so far. Numerous natural peptides with attractive antitumor activity have been isolated from these reservoirs (Table 1). Animal toxins and amphibian skin secretions provide highly efficient molecular "weapons" shaped by natural selection, whereas antimicrobial peptides from the immune system embody endogenous defense strategies against invading pathogens. Collectively, these natural peptide libraries offer abundant cytotoxic molecules with selectivity and provide a continuous source of inspiration and candidate scaffolds for NDOP development in cancer therapy.

Animal toxins, such as snake, scorpion and bee venoms, are particularly rich in NDOPs [21-23]. These toxins have been refined over millions of years of evolution to support predation and defense, and their core bioactive components include diverse peptides [24]. Many toxin-derived peptides exhibit strong membrane activity and can recognize and disrupt tumor cell membranes, which endows them with significant oncolytic potential and makes them valuable templates for innovative anticancer drug discovery [11]. Habermann and co-workers purified melittin from crude bee venom using electrophoresis and showed that it ac-

Table 1 The name, species, and sequence of representative NDOPs [two C (cysteines) or U (selenocysteine) with the same number form corresponding disulfide/diselenide bond; lowercase letters represent D-type amino acids; Z represents pyroglutamic acid; S_5 represents (S)-2-(4'-pentenyl) alanine; Dip represents (S)-3-amino-3-phenylpropanoic acid].

Peptide name	Source	Amino acid sequence	Specific modification(s)	Ref.
Gomesin	*Acanthoscurria gomesiana*	$ZC_1RRLC_2YKQRC_2VTYC_1RGR\text{-}NH_2$	None	40
Anoplin	*Anoplius samariensis*	$GLLKRIKTLL\text{-}NH_2$	None	41
Ano-3	Anoplin (*Anoplius samariensis*)	$GLS_5KRIS_5TLL\text{-}NH_2$	Stapling modification	11
Melittin	*Apis mellifera*	$GIGAVLKVLTTGLPALISWIKRKRQQ\text{-}NH_2$	None	42
MEL-pep	Melittin (*Apis mellifera*)	$GIGAVLKKLTTGLKALISWIKRKRQQ\text{-}NH_2$	Point mutation	43
Cecropin A	*Bombyx mori*	$RWKLFKKIEKVGRNVRDGLIKAGPAIAVIGQAKSLGK\text{-}NH_2$	None	44
Indolicidin	*Bos taurus*	$ILPWKWPWWPWRR\text{-}NH_2$	None	45
Lactoferricin B	*Human*	$FKC_1RRWQWRMKKLGAPSITC_1VRRAF$	None	46
LTX-315	Lactoferricin (*Human*)	$KKWWKKW(Dip)K\text{-}NH_2$	Point mutation	31
FXY-12	Lactoferricin (*Human*)	$kkwwkkw(dip)k\text{-}NH_2$	Substitution with D-amino acids	10
R-DIM-P-LF11-322	Lactoferricin (*Human*)	$PFWRIRIRRPRRIRIRWFP\text{-}NH_2$	None	47
LL-37	Cathelicidin precursor hCAP18 *(Human)*	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	None	30
EP-100	Luteinizing hormone-releasing hormone (*Human*)	KFAKFAKKFAKFAKKFAKQHWSYGLRPG	Targeted modification	48
Smp24	*Maurus palmatus*	IWSFLIKAATKLLPSLFGGGKKDS	None	49
Pardaxin	*Pardachirus marmoratus*	$GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE\text{-}NH_2$	None	50
Dermaseptin	*Phyllomedusa sauvagii*	ALWKTMLKKLGTMALHAGKAALGAAADTISQGTQ	None	37
Temporin-1Cea	*Rana chensinensis*	$FVDLKKIANIINSIF\text{-}NH_2$	None	39
Tritrpticin	*Sus scrofa domesticus*	$VRRFPWWWPFLRR\text{-}NH_2$	None	51
Tachyplesin Ⅰ	*Tachypleus tridentatus*	$KWC_1FRVC_2YRGIC_2YRRC_1R\text{-}NH_2$	None	16
TPI-Se	Tachyplesin Ⅰ (*Tachypleus tridentatus*)	$KWU_1FRVU_2YRGIU_2YRRU_1R\text{-}NH_2$	Point mutation	52
CyPep-1	Axin2 tumor suppressor protein (*Human*)	$ygrkkrrqrrrgktlrvakaiykryie\text{-}NH_2$	Substitution with D-amino acids	53
Mastoparan	*Vespula lewisii*	$INLKALAALKKIL\text{-}NH_2$	None	54
A6-dMP	Mastoparan (*Vespula lewisii*)	$inlkalaalakkil\text{-}KPSSPPEE\text{-}NH_2$	Targeted modification	55
MP9-aPDL1	Mastoparan (*Vespula lewisii*)	$INLKALAAS_5AKKS_5L\text{-}PLGLAG\text{-}nyskptdrqyhf\text{-}NH_2$	Targeted modification and stapling modification	13
Magainin 2	*Xenopus laevis*	GIGKFLHSAKKFGKAFVGEIMNS	None	36

counts for 40 to 50% of the dry weight of bee venom and is its main active component [25]. They further reported that melittin at 1 μmol·L^{-1} selectively inhibited tumor cell proliferation, although it retained substantial hemolytic toxicity that required further optimization. Braganca and colleagues treated Yoshida sarcoma cells with crude venom from the Indian cobra *Naja naja* and first observed venom-induced cell lysis, attributing this effect to a component that was temporarily named cobra venom factor [26, 27]. Subsequently, Wang et al. purified two active components, CTX-I and CTX-III, from *Naja naja* venom and demonstrated that they exerted significant antitumor effects *in vitro* and acted synergistically with phospholipase A2 to lyse tumor cells [28].

The host immune system is another rich natural reservoir of prototypes for NDOPs. Endogenous antimicrobial peptides such as defensins and members of the cathelicidin family form the first line of defense against pathogenic microorganisms [29]. LL-37 is a 37-amino acid peptide generated by proteolytic cleavage of the human cathelicidin precursor hCAP18. It is a core effector of innate immunity and barrier defense and exhibits both antitumor and antibacterial activities [30]. Additionally, LTX-315, which has completed several phase II clinical evaluations, was derived from the cationic antimicrobial peptide lactoferricin B, which is produced by pepsin digestion of bovine lactoferrin [31]. Lactoferricin B is an important component of innate immunity in humans and animals, displays pore-forming activity on bacterial membranes, and shows cytotoxicity toward a variety of tumor cells [32].

Amphibian skin secretions, for example those from frogs and toads, also provide a prolific source of NDOPs with potent activity [33]. To survive in moist habitats that are rich in microorganisms, amphibian skin has evolved to secrete a complex cocktail of chemicals that includes thousands of peptides with antimicrobial, antifungal, and antiviral activities [34, 35]. NDOPs identified and further optimized from these secretions (e.g., magainins [36], dermaseptins [37, 38], and temporin-1CEa [39]) often display a low propensity for resistance development and high selectivity for tumor cells. These properties have made amphibian-derived NDOPs one of the most active areas of research in the field.

2.2. Structural features of NDOPs

Although NDOPs display diverse sequences and originate from a wide range of sources, their oncolytic activity depends on specific three-dimensional conformations (Fig. 1). Based on secondary structure, NDOPs can be broadly grouped into two major families: the α-helix and the β-sheet. A smaller subset of cyclic or structurally disordered peptides, such as tritrpticin [51] and indolicidin [45], is often regarded as having no regular secondary structure. The formation of non-α/β structures does not rely on hydrogen bonding networks among amino acid residues, thereby hindering folding into well-defined secondary structural elements [56].

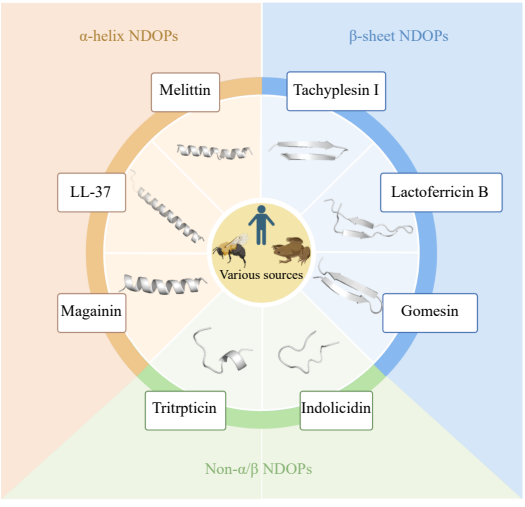

Fig. 1 Structural classification and representative structures of NDOPs.

From a structure–activity relationship (SAR) perspective, the features of α-helical NDOPs provide critical guidance for rational design. This family is exemplified by wasp venom anoplin, frog skin-derived magainins, snake venom cathelicidins, and the human host defense peptide LL-37 [30, 41, 44, 54]. These peptides are typically enriched with hydrophobic residues (e.g., Leu and Ile) and cationic residues (e.g., Lys and Arg), forming well-defined amphipathic helices that are central to their mechanism of action [57, 58]. In aqueous solution, free α-helical NDOPs usually exist as unstructured random coils. Upon encountering anionic model lipid bilayers or tumor cell membranes, they undergo a critical coil-to-helix transition, which enables productive membrane interaction and is a key determinant of their selectivity and potency [58]. The stability of these helices is maintained primarily through intramolecular hydrophobic interactions and hydrogen bonding networks [59]. Representative SAR studies on NDOP analogs indicate that a stable α-helical conformation together with an expanded hydrophobic network on the nonpolar face correlates positively with oncolytic activity, whereas retaining four cationic residues along the peptide chain appears to be an important prerequisite for maintaining acceptable safety margins. Consequently, strategic modifications aimed at enhancing helicity are common design strategies, such as substituting helix-destabilizing residues with helix-promoting ones or employing chemical stapling [11]. Even in these optimized designs, the relationship between helicity and activity is not strictly linear. Excessively high α-helicity can reduce selectivity by increasing nonspecific binding to erythrocyte membranes and thereby elevate the risk of hemolysis [60]. This underscores the importance of a balanced design approach that optimizes potency while maintaining a favorable therapeutic index.

While α-helices dominate the landscape of NDOPs, β-sheet peptides represent a structurally distinct and increasingly important class. Recently identified β-sheet NDOPs, including tachyplesins, lactoferricin, and gomesin, contain at least two cysteine residues that form intramolecular disulfide bonds through oxidative folding [16, 40, 46]. This process generates a rigid antiparallel β-sheet scaffold that confers high conformational stability. From a design standpoint, this disulfide-stabilized architecture is a defining SAR feature because it enforces a different mode of membrane interaction compared with the more dynamic insertion of α-helices. β-sheet peptides often assemble into higher-order structures that disrupt membrane integrity through transmembrane β-barrel-like pores, and their constrained conformations contribute to enhanced resistance to proteolytic degradation, a major advantage for in vivo applications where serum stability is a key limitation [61]. At present, SAR analyses of β-sheet NDOPs have focused mainly on the stabilizing role of disulfide bonds, whereas the rules governing the spatial distribution of hydrophobic and cationic residues and overall amphipathicity remain to be fully elucidated.

Classification of NDOPs according to secondary structure not only facilitates mechanistic understanding but also provides a practical framework for SAR-guided design, modification, and optimization of natural peptide scaffolds to generate NDOPs with higher selectivity and lower toxicity.

3. Antitumor mechanisms of NDOPs

3.1. Direct cell membrane lysis-mediated antitumor effects

NDOPs exploit differences in membrane composition and

structure between normal and tumor cells to achieve selective killing (Fig. 2A). Tumor cells typically display a higher density of negative charge on the outer leaflet of the plasma membrane, which strengthens electrostatic attraction between cationic NDOPs and malignant cells [62, 63]. This increased negative charge arises from several factors, including altered phospholipid composition that exposes more negatively charged phospholipids such as phosphatidylserine on the outer leaflet [64, 65], elevated metabolic activity that leads to increased lactate secretion [62, 66], higher levels of surface sialic acids [67], and changes in membrane glycolipids and glycoproteins [68].

In addition to altered surface charge, tumor cells often exhibit increased membrane roughness compared with normal cells. Abnormal reorganization of the cytoskeleton, including microfilaments and microtubules, promotes the formation of membrane ruffles and protrusions [69, 70]. These morphological changes expand the accessible membrane area for NDOPs. Because peptide-induced membrane disruption is a concentration-dependent process, a larger surface area facilitates peptide adsorption and helps local peptide density reach the threshold required for membrane rupture [71]. Another factor that contributes to selectivity is plasma membrane fluidity. Many malignant cell lines, such as those derived from lung cancer, lymphoma, and glioma, display increased membrane fluidity. Cholesterol is a key regulator of membrane fluidity [72], and changes in cholesterol content in tumor cell membranes can markedly affect this property [73]. Concurrently, metabolic activity in tumor cells, particularly altered fatty acid synthesis and related pathways, often increases the unsaturation of membrane lipids and further promotes membrane fluidity. In contrast, normal eukaryotic cells such as red blood cells contain high levels of sterols in their membranes. These sterols hinder the insertion of membrane-bound NDOPs into the inner region of the lipid bilayer and thereby enhance the tolerance of normal cells. However, some cancer cells, for example certain hepatocellular carcinoma cell lines, may exhibit lower membrane fluidity than their normal counterparts because of reduced fatty acid unsaturation and increased cholesterol content [74].

After electrostatic binding to tumor cell membranes, NDOPs can disrupt membrane integrity through several distinct models and ultimately trigger rapid cell lysis and death. The most widely discussed models include the barrel-stave model, the toroidal-pore model, the carpet model, and other related models (Fig. 2B).

3.1.1. Barrel-stave model

In the barrel-stave model, NDOPs initially bind to the tumor cell membrane as monomers *via* electrostatic attraction. When their local concentration reaches a critical level, the peptides undergo a conformational change and assemble into barrel-like oligomers. Their hydrophobic regions insert vertically into the hydrophobic core of the lipid bilayer, while their hydrophilic regions face the interior of the pore [75]. The peptides thus act like the staves of a barrel, creating discrete transmembrane channels [76]. NDOPs such as melittin and cecropin B adopt α-helical conformations that insert into membranes with their hydrophobic faces oriented toward lipid tails and their hydrophilic faces lining the pore. This process disrupts membrane potential and integrity and ultimately causes membrane rupture and necrosis [77].

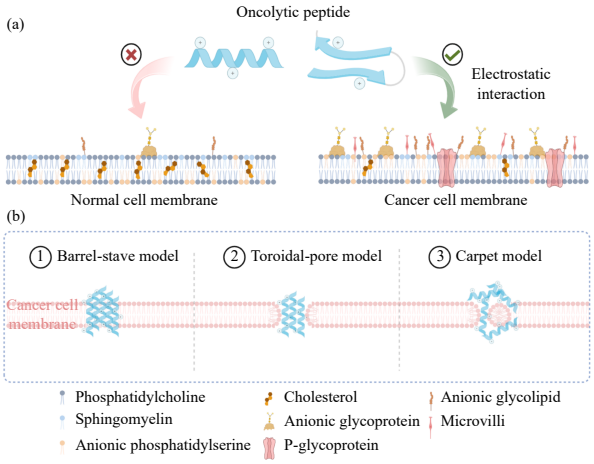

Fig. 2 Direct cell membrane-lysis mechanisms of NDOPs. (A) Representation of key differences between normal and cancer cell membranes. (B) Representative models of NDOP-induced cell membrane disruption.

3.1.2. Toroidal-pore model

The toroidal-pore model is a multi-step process. NDOPs initially bind parallel to the membrane surface through electrostatic interactions. Once a threshold surface concentration is reached, the peptides reorient and insert into the bilayer. They bend the lipid monolayers continuously so that the hydrophilic regions of the peptides and the polar headgroups of lipids from both leaflets together line the pore [78-80]. The resulting toroidal pores span the membrane and allow leakage of cellular contents, leading to tumor cell death. This model is often used to describe the action of relatively short NDOPs. For example, protegrins can induce toroidal pores that perturb membranes and promote pore disintegration [42].

3.1.3. Carpet model

In the carpet model, NDOPs remain aligned parallel to the membrane and cover the tumor cell surface in a carpet-like fashion without initially inserting into the bilayer. As peptide density increases, the surface tension of the membrane rises, and local curvature and lipid packing are disturbed [81-83]. Once a critical concentration is reached, the peptides disrupt phospholipid organization in a detergent-like manner. Transient toroidal pores may form and facilitate further peptide entry into the membrane. When membrane tension exceeds a critical limit, the bilayer collapses and can fragment into micelle-like structures, causing rapid leakage of intracellular contents and cell death [78, 84]. LL-37 is a representative example that can rapidly lyse many tumor cell types through the carpet mechanism [85].

3.1.4. Other membrane-disruption models

In addition to these three major models, several other mechanisms have been proposed to explain NDOP-induced membrane disruption. These include the aggregate model, the sinking-raft model, the molecular electroporation model, and the leaky-slit model [56, 86, 87]. These mechanisms are not mutually exclusive, and a single NDOP may possess more than one mode of action. For instance, magainin has been reported to lyse tumor cell membranes through a combination of carpet, toroidal-pore, and aggregate mechanisms to achieve rapid oncolysis [88, 89]. Moreover, different peptide concentrations can favor different modes of membrane disruption [90]. The precise determinants of these transitions remain incompletely understood and require further mechanistic investigation.

3.2. Non-cell membrane-mediated antitumor mechanisms

Although electrostatic binding to and lysis of tumor cell membranes are central to the antitumor activity of NDOPs, many peptides also engage additional mechanisms that further magnify their efficacy. These include targeting and disrupting intracellular organelle membranes, inducing ICD, modulating immune cells, regulating immune checkpoints, and reprogramming tumor metabolism (Fig. 3).

3.2.1. Organelle targeting

After internalization into tumor cells, NDOPs can bind select-

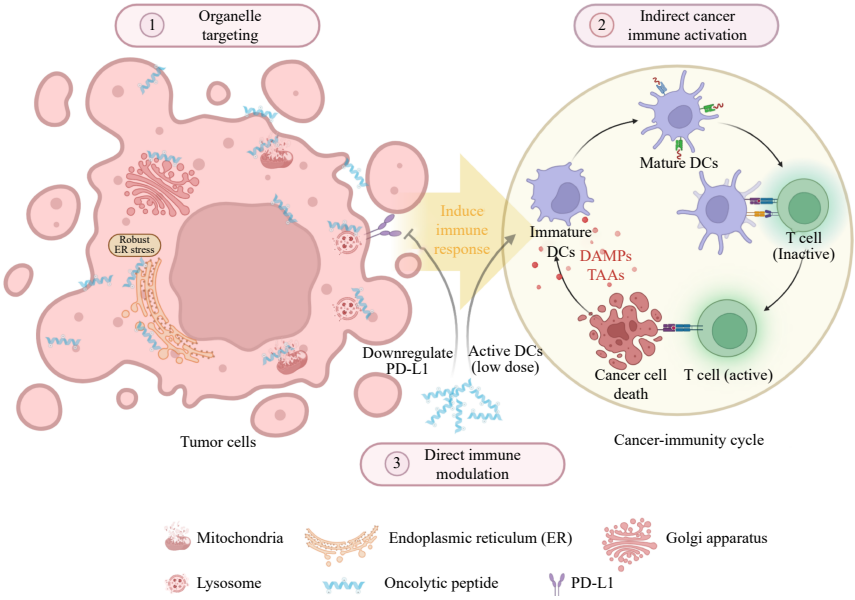

Fig. 3 Schematic diagram illustrating the non-cell membrane-mediated antitumor mechanisms of NDOPs.

ively to intracellular organelle membranes and thereby promote apoptosis and necrosis [15]. Organelle targeting is an important contributor to the rapid and potent oncolytic activity of many NDOPs. The endoplasmic reticulum (ER) is a critical organelle target because it coordinates protein synthesis and folding, lipid biosynthesis, and calcium storage, and disruption of ER homeostasis can directly promote disease [91, 92]. Pardaxin is an NDOP with strong ER-targeting capacity [50, 93]. Pardaxin-modified cationic liposomes are internalized into tumor cells mainly through caveolae-mediated endocytosis, bypass lysosomal degradation and accumulate in the ER [94]. Qin et al. reported that pardaxin-modified cationic liposomes induced significantly higher levels of apoptosis than control formulations such as empty liposomes or naked plasmid [95]. Mitochondria are another particularly important target. NDOPs that accumulate on mitochondrial membranes reduce the mitochondrial membrane potential, impair respiratory function, and trigger bursts of reactive oxygen species (ROS) [96]. These events activate the Bax- and Bcl-2-regulated mitochondrial apoptosis pathway and promote the release of cytochrome c into the cytosol. Cytochrome c then initiates caspase activation, DNA damage, and structural collapse of the cell, which ultimately results in apoptosis [97]. This mitochondrial-dependent mechanism has been observed in lung, colorectal, and melanoma models. Melittin and LTX-315 induce mitochondrial apoptosis by driving ROS production, disrupting the mitochondrial membrane potential, and upregulating cytochrome c, Bax, caspase-3, and caspase-9 in tumor cells [98, 99]. The Golgi apparatus is a central node in the intracellular membrane network and regulates protein modification, sorting and trafficking, and its dysfunction is closely linked to metabolic disorders and cancer progression [100]. R-DIM-P-LF11-322 is an NDOP derived from lactoferricin. In addition to rapidly lysing the plasma membrane, R-DIM-P-LF11-322 selectively accumulates in the Golgi apparatus, disrupts Golgi structure, triggers mitochondrial swelling, and induces apoptosis, leading to potent antitumor effects in mouse melanoma models [47]. LTX-401 is an amphiphilic NDOP incorporating $\beta^{2,2}$-amino acids. Beyond its capacity to induce rapid cell membrane lysis, LTX-401 selectively accumulates in the Golgi apparatus, thereby disrupting its structural integrity and triggering a caspase-independent yet partially mitochondria-dependent cell death pathway, which collectively contributes to its potent antitumor efficacy in murine melanoma models [101]. Furthermore, LTX-401 has been shown to bind to lysosomal membranes in melanoma cells, compromising lysosomal integrity and contributing to the induction of cell death [102].

3.2.2. Indirect cancer immune activation

Among non-membrane mechanisms, indirect immune activation through ICD and re-engagement of the cancer-immunity cycle (CIC) appears to be the most consistently observed and is likely the main driver of durable systemic responses to NDOP therapy [103]. NDOP-driven ICD has been documented for both α-helical NDOPs, including anoplin and LTX-315, and β-sheet NDOPs such as tachyplesin, and is a key determinant of long-term antitumor immunity *in vivo* [52, 55]. Unlike many classical ICD inducers, the protective immune effects mediated by NDOPs depend on various signaling pathways, such as the type I interferon 1α/β receptor/toll-like receptor 3 (TLR3) and high mobility group protein 1 (HMGB1)/TLR4 pathways [104]. During NDOP-driven oncolysis, tumor cell death is highly immunogenic. Dying cells release tumor antigens together with a suite of chemotactic and immunostimulatory signals, collectively known as damage-associated molecular patterns (DAMPs), including calreticulin (CRT), adenosine triphosphate (ATP), HMGB1, and heat shock proteins such as heat shock protein 70 and heat shock protein 90 [104-106]. As a "find me" signal, extracellular ATP binds to ionotropic (P2X7) and metabotropic (P2Y2) purinergic receptors on antigen-presenting cells (APCs), thereby stimulating their maturation and inducing chemotaxis. Furthermore, extracellular ATP activates the caspase-1-dependent NLRP3 inflammasome to promote interleukin-1β secretion [107, 108]. CRT acts as an "eat me" signal that recruits APCs, particularly dendritic cells (DCs), and promotes phagocytosis of tumor debris [109]. These loaded APCs then mature and migrate to tumor-draining lymph nodes or tertiary lymphoid structures, where they efficiently present processed tumor antigens to naïve T cells [110]. This process primes and activates tumor-specific cytotoxic T lymphocytes. The activated T cells traffic back to and infiltrate the tumor microenvironment (TME), recognize antigen-expressing tumor cells, and kill them, thereby initiating a new round of the CIC [111]. The systemic propagation of this cycle underpins the local and distant antitumor effects observed in NDOP models and enables NDOPs to control not only primary lesions but also metastatic disease [15, 109]. By forcefully initiating the CIC, NDOPs can convert immunologically "cold" tumors into "hot" tumors, overcome local immunosuppression, and establish durable systemic immune memory, highlighting their promise as in situ cancer vaccines [112].

3.2.3. Direct immune modulation

The direct immune-modulatory activities of NDOPs represent a significant and non-negligible secondary mechanism contributing to their overall antitumor efficacy. Notably, when NDOPs are administered *via* intratumoral injection, these peptides demonstrate selective activity within the TME. NDOPs exhibit higher affinity for tumor cells and bind to immune cells or normal cells at lower concentrations, thereby exerting immunostimulatory effects with reduced adverse effects. For instance, at low concentrations, LTX-315 can directly activate TLR7 in a MyD88-dependent manner. This activation engages downstream signaling pathways, including NF-κB and MAPK, and promotes inflammasome assembly, collectively driving DC maturation and functional activation [113]. The second pathway by which LTX-315 or LL-37 induces DC maturation entails the complex formation between LTX-315 and nucleic acids (DNA and RNA) [113, 114]. Beyond triggering the release of nucleic acids from dying cancer cells, LTX-315 binds to these molecules and forms stable complexes. These complexes are protected against degradation and can therefore more readily access DC endosomes. This facilitates an enhanced capacity to induce maturation in DCs co-expressing TLR8 and TLR9 [115]. Additionally, LTX-315 remodels the immunosuppressive TME by selectively reducing the abundance of intratumoral regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), two key cell populations that inhibit antitumor immunity. Furthermore, its antitumor activity has been shown to operate in a natural killer cell-dependent manner, highlighting its capacity to engage innate immune effector mechanisms [104, 116].

NDOPs may also modulate immune checkpoints and thereby reshape the TME [117]. LTX-315 has been shown to promote lysosome-dependent degradation of PD-L1 by inhibiting the ATP11B/CMTM6 complex, which reduces PD-L1 expression on the surface of pancreatic tumor cells and relieves inhibition of T cells [118]. Specifically, LTX-315 suppresses the expression of the transmembrane ATPase ATP11B in pancreatic cancer cells in dose- and time-dependent manners. ATP11B, as a key regulator of PD-L1 expression, endogenously interacts with PD-L1 in a CKLF-like MARVEL transmembrane domain-containing 6 (CMTM6)-dependent manner. CMTM6 acts as an adaptor protein that mediates the endosomal recycling of PD-L1, thereby preventing its lysosomal degradation. The synergistic action between ATP11B and CMTM6 further enhances PD-L1 stability, maintaining high PD-L1 expression on the tumor cell surface. This subsequently inhibits T cell activation *via* the PD-1/PD-L1 pathway, promoting tumor immune evasion. Following the downregulation of ATP11B by LTX-315, its positive regulatory effect on CMTM6 is attenuated, leading to a decrease in CMTM6 levels. Consequently, the endosomal recycling of PD-L1 is disrupted, resulting in its lysosomal degradation. This ultimately leads to a significant reduction in PD-L1 surface expression on pancreatic cancer cells, thereby alleviating the PD-1/PD-L1 pathway-mediated immune suppression. In conjunction with LTX-315-mediated T cell activation, cytokine secretion, and related pathways, these effects collectively enhance lymphocyte infiltration and the antitumor immune response. Overall, these direct immune-modulatory effects complement the primary oncolytic activity, enhancing systemic antitumor immunity while maintaining a favorable selectivity profile toward malignant cells and tumor-associated stroma over healthy tissues.

3.2.4. Other mechanisms

In addition, some NDOPs exert antitumor effects by targeting intracellular processes and TME-relevant pathways. Their mechanisms include cytoskeleton disruption, reprogramming of glucose and lipid metabolism, and regulation of metastasis- and apoptosis-related signaling pathways, which may contribute to the suppression of tumor growth and metastasis. 1) Disruption of the tumor cell cytoskeleton. Smp24, an NDOP isolated from the venom gland of the Egyptian scorpion *Maurus palmatus*, shows preferential antitumor activity with low cytotoxicity to normal cells [49]. Mechanistically, it binds to and depolymerizes F-actin, disrupting cytoskeletal integrity and inducing cell-cycle arrest. It also modulates extracellular matrix remodeling by downregulating the expression and gelatinolytic activity of matrix metalloproteinase (MMP)-2 and MMP-9, while upregulating tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2, thereby shifting the MMP/TIMP balance toward reduced matrix degradation and impaired tumor cell migration and invasion. 2) Reprogramming of glucose and lipid metabolism. Melittin has been reported to remodel tumor metabolism and angiogenesis-associated signaling. It upregulates the tumor suppressor LATS2, suppressing the activity of the oncogenic co-activators YAP and HIF-1α, which in turn reduces the transcription of glycolytic enzymes and vascular endothelial growth factor, thereby attenuating the Warburg effect and tumor angiogenesis [119]. In parallel, melittin interferes with lipid metabolism by downregulating key lipogenic enzymes (e.g., fatty acid synthase and acetyl-CoA carboxylase) through the suppression of the master transcription factor sterol regulatory element-binding protein 1 [120]. 3) Regulation of metastasis- and apoptosis-related pathways. Beyond metabolic regulation, melittin also impacts oncogenic signaling nodes implicated in metastasis and survival. It disrupts the SDF-1α/CXCR4 axis, a critical pathway for tumor cell homing and metastasis, inhibits the Wnt/β-catenin pathway to reduce cell proliferation, and suppresses the JAK2/STAT3 pathway to promote apoptosis and inhibit survival signals [121-123]. These examples highlight that selected NDOPs can engage multiple non-membrane targets and pathways, providing mechanistic rationale for their multi-level antitumor activity.

Notably, although NDOPs can kill tumor cells *via* membranelytic and intracellular mechanisms, adaptive desensitization or resistance cannot be fully excluded. Reported resistance is mainly associated with tumor cell membrane remodeling, especially reduced anionic components (such as O-linked glycosylation, sialylation, and proteoglycan metabolism), which weakens NDOP binding and electrostatic engagement, leading to low-to-moderate shifts in IC_{50}/EC_{50} (about 3−5-fold) [124, 125]. The acquisition of such phenotypes typically requires months to a year of stepwise dose escalation and is often constrained at elevated peptide concentrations, indicating a restricted adaptive landscape for strictly lytic mechanisms. Moreover, the development of resistance may incur fitness costs, as peptide-resistant variants showed a significant reduction in tumorigenic potential *in vivo* [124]. In a more conventional resistance-induction window (constant IC_{50} dose for up to 4 weeks), Chen et al.[126] observed no morphological changes or IC_{50} shifts after lytic peptide treatment, whereas doxorubicin (DOX) rapidly induced resistance. Overall, NDOPs appear less prone to classical resistance than many chemotherapeutics, but membrane/glycocalyx remodeling should be monitored.

4. Innovative therapeutic applications of NDOPs

NDOPs have become an active area of cancer research because of their high selectivity for tumor cells and their low propensity to induce resistance. However, as single agents, their efficacy is often limited by a short plasma half-life and the immunosuppressive TME. Rational combination strategies can therefore markedly enhance their therapeutic potential (Fig. 4).

4.1. Combination with chemotherapy

Classical chemotherapeutic agents must enter tumor cells to

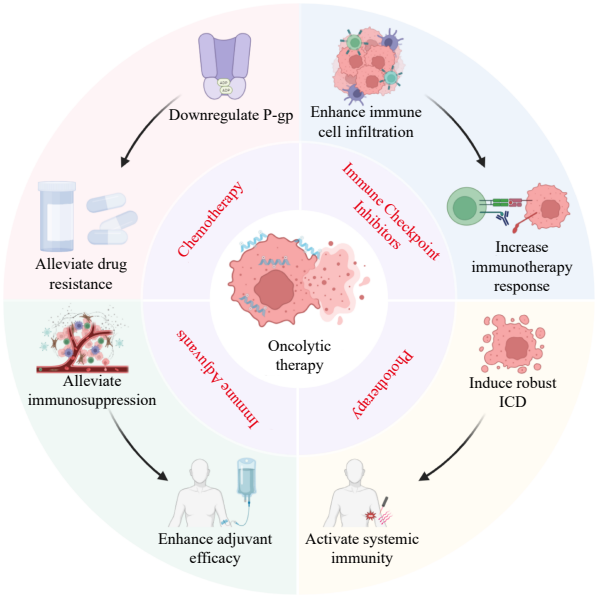

Fig. 4 Combination strategies involving NDOP-based therapy.

exert their effects, which often results in low intracellular drug exposure, rapid systemic clearance, and the need for frequent or high-dose administration. These features contribute to severe adverse effects and frequent resistance [127, 128]. As NDOPs act through multiple mechanisms, they can help overcome chemoresistance and restore sensitivity to conventional drugs. As early as 1992, Ohsaki et al. reported that magainin analogs combined with DOX, cisplatin, or etoposide produced additive inhibition of tumor cell growth [129]. Since then, many NDOPs have been shown to reverse resistance to several chemotherapeutics [15, 130]. Melittin is a representative example, which increases the sensitivity of drug-resistant tumor cells to diverse agents (e.g., cisplatin [131], gemcitabine [132], DOX [133-135], 5-fluorouracil [43], temozolomide [136]) in models of breast, liver and colon cancer cells. Beyond direct cell lysis, melittin interferes with key resistance pathways. One major mechanism involves downregulation of multidrug resistance protein 1 (MDR1/P-glycoprotein, P-gp) and inhibition of upstream signaling pathways, including PI3K/Akt and NF-κB [137]. Because P-gp is a central efflux pump that reduces intracellular concentrations of many anticancer drugs, its inhibition by melittin can restore chemosensitivity [138]. Additionally, melittin has also been reported to modulate multidrug resistance-associated protein 2 and several drug metabolizing enzymes, including CYP1A1, CYP1B1 and GSTP1, which may further contribute to the reversal of chemoresistance [139]. LTX-315 is another NDOP with strong chemosensitizing activity. In pancreatic cancer cell lines, LTX-315 downregulates P-gp indirectly by disrupting the ATP11B-CMTM6-PD-L1 axis and reverses classical multidrug resistance [117]. At the same time, LTX-315 remodels the immunosuppressive TME while reversing resistance. In combination with DOX, LTX-315 increases intratumoral $CD4^+$ and $CD8^+$ T-cell infiltration and produces superior antitumor efficacy in rat hepatocellular carcinoma models compared with either agent alone, without obvious systemic toxicity [140, 141]. Furthermore, some NDOPs also target chemoresistant cells through direct interaction with membrane proteins. For example, the NK-lysin-derived peptide NK-2 co-localizes with P-gp on MDR tumor cell membranes and reduces P-gp transport activity, thereby effectively eradicating P-gp-positive MDR cells within heterogeneous tumors [142].

4.2. Combination with immune checkpoint inhibitors

Immune checkpoint blockade is now a major strategy in clinical oncology. However, in solid tumors, its efficacy remains limited. Response rates are often modest and largely restricted to immunologically "hot" tumors with high mutational burden and pre-existing T-cell infiltration, whereas many microsatellite-stable tumors remain refractory because of low antigenicity and defective antigen presentation [143, 144]. Therefore, rational combination approaches are needed to overcome these intrinsic limitations. NDOPs exert potent oncolytic and immunostimulatory effects and can act as in situ vaccines. They are attractive "potentiators" for immune checkpoint inhibitors, particularly in tumors with historically low response rates to immunotherapy, such as colorectal cancer and triple-negative breast cancer [145, 146]. NDOPs rapidly lyse tumor cells and release large quantities of tumor-associated antigens, which enhances antigen presentation and promotes T cell priming [147, 148]. In parallel, immune checkpoint inhibitors remove inhibitory signals on T cells. Together, these effects strengthen and prolong antitumor immunity and can promote systemic immune memory [149]. In multiple models, this combination significantly enhances the therapeutic efficacy of anti-PD-1 and anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies. Yamazaki et al. further showed that the synergistic interaction between CTLA-4 blockade and LTX-315 was diminished when the β-chain of the interleukin-2 receptor was blocked. This finding indicates that the IL-2/IL-15/CD122 axis is required for the full immunostimulatory effect of anti-CTLA-4 antibodies in this setting [101].

4.3. Combination with immune adjuvants

Immune adjuvants play a distinctive role in cancer therapy. They enhance activation of professional APCs through engagement of pattern recognition receptors (e.g., TLR, STING, and NOD-like receptor agonists), thereby augmenting antigen presentation, upregulating costimulatory molecules (CD80/86), and promoting a proinflammatory cytokine milieu that supports robust tumor-specific $CD8^+$ T-cell priming and immune memory [150]. However, the accumulation of Tregs, MDSCs, and M2-type tumor-associated macrophages creates a strong barrier that impairs DC maturation and antigen presenting capacity through cytokine skewing, metabolic competition and upregulation of coinhibitory ligands [151-153]. Combining NDOPs with immune adjuvants can help overcome these barriers, convert immunologically "cold" tumors into "hot" tumors, and expand the population that benefits from immunotherapy. A key event in NDOP-mediated ICD is the rapid release of ATP. However, the adenosinergic axis (CD39/CD73 pathway) degrades ATP into adenosine, which signals through the adenosine A2A receptor (A2AR) on APCs and T cells and functions as a brake on peptide-driven oncolytic immunotherapy-apy [154, 155]. Wu et al. designed a lipid-coated microsphere (CA@TLM) loaded with a NDOP (PalAno) and an A2AR inhibitor (CPI-444) [156]. PalAno rapidly lyses tumor cell membranes and releases antigens, while CPI-444 blocks adenosine-mediated immunosuppression. This combination produced strong synergistic effects in triple-negative breast cancer and melanoma models, inhibiting both tumor growth and metastasis. Similarly, Guo et al. developed a nano-delivery system that co-loads melittin with the immune adjuvant resiquimod (R848) [157]. Melittin-induced ICD provides abundant antigens and danger signals, whereas R848 further boosts innate and adaptive immune activation. In mice bearing bilateral 4T1 tumors, this nanomedicine elicited potent local and systemic antitumor immunity and suppressed the growth of distant lesions. Nguyen et al. demonstrated that co-delivery of LTX-315 and the TLR3 agonist poly(I : C) also generated a highly immunogenic TME and improved the efficacy of immunotherapy [158].

4.4. Combination with phototherapy

Photodynamic therapy (PDT) is a noninvasive and relatively

low toxicity clinical treatment. The ROS generated during PDT can damage mitochondria and induce ICD [159]. However, existing PDT primarily induces type I ICD, which is less efficient and is often hampered by an immunosuppressive TME following PDT [160]. Critically, incomplete ablation can also leave sublethally damaged tumor cells at the treatment margins. These surviving cells benefit from exacerbated hypoxia and pro-survival signaling, which promotes local recurrence [161]. NDOPs, particularly ER-targeting peptides, can induce stronger type II ICD while alleviating immunosuppression, which helps reduce the risk of recurrence and metastasis during the post PDT interval [55, 162]. On this basis, Ren et al. designed a NDOP-based conjugate (A6-dMP-VP) for combination with PDT, which provided superior control of both primary and distant tumors compared with PDT or peptide alone [55]. Similarly, Zhang et al. developed a biomimetic nanoparticle, MDM@TPP, that co-loads melittin and the photosensitizer mTHPC [163]. The combination of melittin and PDT synergistically killed tumor cells and induced pronounced ICD and DC maturation, leading to effective inhibition of primary tumor growth, metastasis, and recurrence in 4T1 tumor-bearing mice.

Photothermal therapy (PTT) is another promising local treatment with high selectivity, minimal invasiveness, and the capacity to induce antitumor immunity. Its efficacy is often limited by shallow laser penetration and insufficient release of tumor antigens, which can result in recurrence and metastasis [164]. NDOPs complement PTT because they can efficiently ablate tumors, release abundant antigens, and relieve immunosuppression. For example, Gao et al. constructed a nano-drug delivery system (A3@GMH) co-delivering stapled anoplin and the photothermal material graphene oxide [41]. A3@GMH promotes 4T1 cell lysis, lactate dehydrogenase release, and ICD. When combined with PTT, it strongly inhibited tumor growth in orthotopic 4T1 models, achieving an 88.9% tumor inhibition rate without obvious systemic toxicity.

4.5. Multimodal combination strategies

Combining NDOPs with both chemotherapy and immunotherapy can create a triple synergistic mechanism that markedly enhances antitumor efficacy and helps overcome the limitations of monotherapies. The cationic nature of many NDOPs allows them to form electrostatic complexes with anionic drugs, so they can function as self-assembled carriers that improve intracellular delivery, facilitate lysosomal escape, and augment ICD. Zhang et al. designed a carrier-free nanoparticle based on a prodrug fluorination strategy to co-deliver DOX, a melittin prodrug, and an antitumor small interfering RNA (siTOX; TOX, thymocyte selection-associated HMGB protein) [165]. The targeted release of DOX and the melittin prodrug directly kills tumor cells and exposes DAMPs, promoting DC maturation and antigen presentation, and thereby further increasing $CD8^+$ T-cell infiltration into the tumor. In parallel, siTOX downregulates TOX in T cells, alleviates $CD8^+$ T cell exhaustion and further boosts T-cell infiltration and function. These coordinated pathways strongly inhibited liver metastasis of hepatocellular carcinoma and breast cancer *in vivo*.

5. Clinical progress of NDOPs

With the combined advantages of rapid membrane lysis and potent immune activation, NDOPs have progressed quickly from preclinical studies into clinical testing and are regarded as important candidates for next-generation cancer immunotherapy. To date, four NDOPs (LTX-315, EP-100, CyPep-1, and LL-37) have entered clinical development. Three of them have completed-phase II or phase I/II studies, highlighting NDOP-based therapy as a promising strategy for cancer treatment and cancer immunotherapy (Table 2).

LTX-315 is the most clinically advanced NDOP and has completed several phase II trials with encouraging antitumor activity. Developed by Lytix Biopharma, LTX-315 is a first-in-class oncolytic peptide designed for intratumoral administration as an in situ vaccine that elicits patient-specific immune responses against tumor antigens. In a phase II trial in basal cell carcinoma (NCT05188729), 86% of LTX-315-treated patients (n = 93) showed marked tumor shrinkage and 51% achieved complete lesion clearance, with no dose-limiting toxicities or serious treatment-related adverse events reported. In another phase II study in metastatic soft tissue sarcoma (NCT03725605), LTX-315 combined with adoptive T-cell therapy induced strong tumor-specific immune responses, and tumor-reactive T cells could be expan-

Table 2 Ongoing and completed clinical trials of NDOP therapeutics in cancer.

Agent	Conditions	Phase	Status	Combination	NCT number	Key efficacy outcomes
LL-37	Melanoma	I/II	Completed	Monotherapy	NCT02225366	Well tolerated, except 1 discontinuation due to lack of efficacy
LTX-315 (VP-315)	Transdermally accessible tumors	I	Completed	Monotherapy	NCT01058616	Completed (n = 14); results pending
	Melanoma, breast cancer, head and neck cancer, lymphoma, and triple-negative breast cancer	I	Completed	Use alone or combined with ipilimumab or pembrolizumab	NCT01986426	Tumor reduction ≥ 30% in 29%; elevated intralesional $CD8^+$ T cells in 86% (12/14)
	Carcinoma	I	Completed	Combined with a cancer vaccine (GV1001)	NCT01223209	Completed (n = 12); results pending
	Advanced melanoma	II	Recruiting	Combined with pembrolizumab	NCT04796194	Well tolerated; overall response rate 14%
	Basal cell carcinoma	II	Completed	Monotherapy	NCT05188729	Marked tumor shrinkage in 86% (n = 93); complete clearance in 51%
	Advanced soft tissue sarcoma	II	Completed	Combined with adoptive T-cell therapy	NCT03725605	Well tolerated; best response: stable disease (208 days)
	Melanoma stage IIIB-IV	II	Recruiting	Combined with Pembrolizumab	NCT06651151	Ongoing (n = 27); final results expected May 2026
CyPep-1	Advanced solid tumor malignancy	I/II	Completed	Use alone or combined with pembrolizumab	NCT04260529	Overall response rate 50% (3/6) with CyPep-1 monotherapy; 2 durable responses > 6 months; induced cancer cell death > 70%
	Advanced head and neck squamous cell carcinoma, advanced breast cancer, and advanced melanoma	I/II	Completed	Use alone or combined with pembrolizumab	NCT05383170	Serious adverse event in 1/6 patients (16.7%, erysipelas)
EP-100	Advanced solid tumors	I	Completed	Monotherapy	NCT00949559	Well tolerated; durable stable disease ≥ 16 weeks in 19%
	Ovarian cancer	II	Completed	Monotherapy or combined with paclitaxel	NCT01485848	Well tolerated; overall response rate 69% *vs* 16% with paclitaxel monotherapy in liver metastases patients

ded ex vivo from lesions pretreated with LTX-315 [18]. The regimen was safe and well tolerated, although further optimization is required to maximize clinical benefit. A phase II trial of LTX-315 in combination with pembrolizumab in advanced melanoma (NCT04796194) is currently ongoing [166]. In a prior phase I/II study (NCT01986426), the combination of LTX-315 and pembrolizumab showed notable clinical activity, with 29% of patients experiencing at least 30% shrinkage of injected lesions and 86% of evaluable biopsies showing increased intralesional $CD8^+$ T cells after treatment [167]. Overall, LTX-315 has been evaluated in seven clinical trials across multiple indications, including melanoma, breast cancer, head and neck cancer, lymphoma, basal cell carcinoma, and soft tissue sarcoma, demonstrating a favorable safety profile and broad antitumor potential.In addition, LL-37 has completed a phase I trial (NCT02225366) assessing intratumoral dosing in melanoma patients, with no serious adverse events reported in any patient following treatment. Besides LTX-315 and LL-37, two rationally designed synthetic oncolytic peptides (EP-100 and CyPep-1) derived from endogenous human peptide sequences have also entered phase II clinical development. EP-100, developed by Esperance Pharmaceuticals, is an NDOP created by linking an artificial 18-amino acid cationic α-helical lytic peptide to a 10-amino acid sequence derived from natural luteinizing hormone-releasing hormone (LHRH). EP-100 can selectively target tumor cells that express LHRH receptors. In a phase I pharmacodynamic and pharmacokinetic study in patients with advanced solid tumors (NCT00949559), doses of 5.2 mg/m^2 or higher achieved the cell lysis concentrations predicted *in vitro* in 37 LHRH receptor-positive patients, and the maximum tolerated dose was not reached even at 40 mg/m^2 [48]. Only mild to moderate and reversible infusion-related skin reactions were observed, and there were no dose-limiting toxicities. Seven patients (19%) achieved stable disease for at least 16 weeks. A phase II study in recurrent ovarian cancer (NCT01485848) showed that EP-100 at 30 mg/m^2 combined with paclitaxel at 80 mg/m^2 was safe and well tolerated in patients with refractory and recurrent disease, although the overall response rate was similar to that of paclitaxel alone [19]. In the subgroup of patients with liver metastases, the overall response rate was 69% with combination therapy compared with 16% for paclitaxel alone, suggesting that EP-100 may be particularly beneficial for ovarian cancer patients with hepatic lesions. Additionally, CyPep-1 is an NDOP composed of 27 amino acids in an all-*D*-configuration. More broadly, converting *L*- to *D*-amino acids (or introducing partial *D*-substitutions) is a widely used strategy to enhance the proteolytic stability and efficacy of linear oncolytic peptides [10, 168]. Its parent sequence originates from residues 126 to 140 of the tumor suppressor protein Axin2, but this sequence was used mainly as a template for extensive computational and chemical optimization rather than to preserve Axin2 function. Two phase I/II trials (NCT04260529 and NCT05383170) have evaluated CyPep-1 as monotherapy and in combination with the anti-PD-1 antibody pembrolizumab in patients with advanced or metastatic solid tumors, including head and neck squamous cell carcinoma, melanoma, and triple-negative breast cancer [53]. Among six patients with adrenocortical carcinoma receiving CyPep-1 monotherapy, a disease control rate of 50% (n = 3/6) was observed, with durable responses (> 6 months) in two patients. Analyses of paired tumor biopsies demonstrated induction of cancer cell death in > 70% across tumor types. Given the unique antitumor mechanisms of NDOPs, additional agents in this class are likely to enter clinical testing and may help address the unmet need posed by refractory and treatment-resistant cancers.

Despite their preferential targeting of tumor cells, the clinical translation of NDOPs faces significant pharmacological challenges, primarily a narrow therapeutic window and suboptimal pharmacokinetic profiles. Dose-limiting toxicity remains a central concern, including the risk of hemolysis and nephrotoxicity arising from nonspecific electrostatic interactions between cationic peptides and anionic phospholipids on normal cells such as erythrocytes and renal tubular epithelial cells. These off-target effects constrain the maximum tolerated dose and help explain why most clinical-stage NDOPs, including LTX-315, CyPep-1, and LL-37, have so far been evaluated primarily by intratumoral injection. This route is well suited for accessible lesions but offers limited solutions for deeply seated or disseminated metastases. Although NDOPs are expected to be less immunogenic than viral vectors or large biologics, robust data on long-term immunogenicity are still lacking. Within this landscape, EP-100 provides an instructive example of how receptor-mediated targeting can enable systemic administration. As summarized above, EP-100 uses an LHRH-derived motif to concentrate membrane-lytic activity on LHRH receptor-positive tumors while largely sparing normal tissues. This design improves the therapeutic index and has allowed intravenous dosing with mainly mild and reversible infusion-related reactions in early-phase trials. At the same time, the clinical data also highlight the limitations of current NDOP design. EP-100 is built from natural L-amino acids and is rapidly degraded by circulating peptidases, which contributes to its short plasma half-life and necessitates relatively frequent and prolonged infusions to maintain effective exposure. Objective response rates have been modest overall, with clearer benefit emerging only in selected subgroups, such as ovarian cancer patients with liver metastases, underscoring the importance of target expression, tumor heterogeneity, and rational patient selection in future studies.

Based on these pharmacological constraints, recent efforts have focused on engineering strategies to widen the therapeutic index and improve systemic exposure of NDOPs. Nevertheless, systemic administration still requires careful control of off-target blood/tissue interactions. For instance, Tc-labeled melittin showed a rapid drop in blood exposure (to about 1% ID g^{-1} within 10 min) and predominant accumulation in the spleen, liver, and lungs, consistent with red-blood-cell membrane disruption followed by clearance in filtration organs in mice [169]. To overcome these limitations while preserving oncolytic potency, several engineering strategies are being pursued. 1) Prodrug approaches. Through rational chemical modification, key cationic/amphipathic features can be temporarily masked to improve physicochemical properties and reduce off-target interactions, while enabling tumor-local activation and recovery of pharmacological activity. Ren et al. constructed an activatable prodrug peptide that leverages the high glutathione level in the TME for in situ activation, increasing tumor enrichment by 2.5-fold, with this enhanced distribution pattern persisting for up to 48 h after intravenous administration [55]. 2) Targeted modification strategies. By conjugating targeting ligands to NDOPs, NDOPs can acquire the ability to recognize tumor-associated surface markers, thereby increasing selective cytotoxicity while reducing collateral damage. Lu et al. developed a novel conjugate (PEG-MP9-aPDL1) based on mastoparan by integrating a 4-arm PEG, an MMP-2-cleavable linker, and a PD-L1-targeting peptide [13]. In this conjugate, the targeting moiety promotes preferential accumulation and penetration in PD-L1-high tumors while limiting injury to normal tissues. Notably, the PD-L1-binding peptide can also provide checkpoint-blockade-like immunomodulation, offering potential synergy beyond improved tumor delivery. 3) Novel delivery strategies. Intelligent nanocarrier-mediated delivery approaches have been designed to enable passive or active targeting and reduce nonspecific membrane interactions, which is particularly relevant for relapsed and refractory cancers [86, 170]. Yu et al. developed a high-density lipoprotein nanoparticle to load melittin, forming α-melittin-NP; compared with free melittin, α-melittin-NP markedly reduced hemolytic toxicity, shielded anti-

gen-presenting cells from peptide damage, and still preserved tumor-killing activity, ultimately eliciting a systemic antitumor immune response. Taken together, intratumoral injection remains the most mature and commonly used clinical administration route, as it can elicit local oncolysis and systemic immunity while controlling systemic toxicity. However, advancing systemic administration routes (e.g., intravenous and potentially oral delivery) remains an important frontier for NDOPs; EP-100 illustrates both the promise and the practical barriers of this transition. Continued progress will likely depend on integrating tumor-restricted activation, molecular targeting, and advanced delivery systems, together with rigorous clinical validation.

6. Summary and outlook

This review has summarized the sources, structural features, mechanisms, combination strategies, and clinical progress of NDOPs. NDOPs not only lyse tumor cell membranes directly but also engage multiple non-membrane mechanisms, including organelle targeting, induction of ICD, modulation of immune cells, and regulation of immune checkpoints. Through this coordinated network of effects, NDOPs can convert immunologically "cold" tumors into "hot" tumors, generate in situ vaccine-like activity, and substantially improve responses when combined with conventional therapies. As their mechanisms are progressively clarified, the unique position of NDOPs at the interface of membrane biology, innate immunity, and cancer immunotherapy is becoming clearer, which in turn is accelerating their clinical translation.

Despite this progress, a major translational bottleneck, driven by limited tumor selectivity and non-specific biodistribution during systemic exposure, still constrains the therapeutic window of many NDOPs and hinders their transition from local injection to broadly applicable systemic regimens (discussed in detail in Section 5). Within this context, three key questions remain: How can NDOPs be discovered and optimized more efficiently? How can they be produced at scale in a cost-effective manner? How can their molecular mechanisms be defined in sufficient detail to guide rational clinical use?

First, on the discovery side, current routes that rely on stepwise isolation from natural sources and empirical sequence modification remain slow and labor-intensive. Machine learning and artificial intelligence offer a way to streamline this process by learning sequence-to-activity and sequence-to-toxicity relationships, narrowing the experimental search space, and enabling de novo design of new NDOPs. Given the shared cationic/amphipathic design principles and membrane-interaction readouts between antimicrobial peptides and NDOPs, AMP-focused AI pipelines provide a practical template for NDOP discovery and optimization. For example, Torres et al. employed AI tools (such as the AmPEP random-forest classifier and the SmORFinder deep-learning model) to prioritize 323 candidate peptides with potential antimicrobial activity from 444,054 small-protein families [171]. Beyond screening, generative AI frameworks are increasingly being used for de novo peptide design, for instance by integrating pretrained protein language models with diffusion/generative models to directly propose new bioactive sequences for experimental testing [172]. These representative examples in antimicrobial peptides provide a useful blueprint for NDOP design.

Second, scalable preparation of NDOPs remains a major bottleneck. Direct extraction from natural materials is limited by scarce supply and complex purification, while solid-phase peptide synthesis is expensive and often yields poorly for longer or heavily modified peptides that require multiple chromatographic steps [173, 174]. A shift toward innovative bioproduction platforms is therefore critical. Synthetic biology and advanced genetic engineering are being used to express challenging peptides in microbial hosts. For example, yeast secretion platforms (e.g., Pichia pastoris/Komagataella phaffii) are particularly attractive for disulfide-rich or conformationally constrained peptides, as they provide an oxidizing secretory environment that supports correct folding and can be coupled with downstream enzymatic maturation for cyclic scaffolds [175], providing a potential design strategy for the large-scale production of NDOPs.

Third, the subcellular fate and molecular targets of many NDOPs are still incompletely defined. For most clinical and preclinical candidates, it remains unclear which membrane components, organelles, or signaling pathways dominate their efficacy and toxicity in different tumor types. Applying advanced biophysical and analytical tools, such as surface plasmon resonance, mass spectrometry-based interactomics, bio-layer interferometry, and backscattering interferometry, together with live-cell imaging, organelle-specific probes, and multi-omics profiling should help clarify intracellular distribution, ICD induction, and TME remodeling. In-depth target analysis can reveal the molecular basis for tumor-selective killing, guide the design of targeted, bifunctional NDOPs, and enable biomarker-driven patient stratification to optimize dosing and avoid ineffective treatment [55].

Addressing these interrelated challenges in discovery, manufacturing, and mechanistic elucidation will be essential to move NDOPs from locally injected experimental tools toward systemically delivered, broadly accessible, and clinically viable anticancer therapeutics.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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