Review

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Virus-Like Particle Nanocarriers for Precision Chemotherapy

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Abstract

Virus-like particles (VLPs) are self-assembling protein nanostructures that replicate the structural precision of viral capsids while lacking genetic material, rendering them inherently safe and highly modular biomaterials. Their genetically encoded architecture enables precise control over size, symmetry, mechanical stability, surface topology, and internal cavity volume, positioning VLPs as programmable protein-based nanocarriers for chemotherapeutic delivery. Recent advances in capsid engineering, biorthogonal conjugation, and template-guided assembly have enabled fine tuning of cargo loading, targeting ligand display, and stimuli-responsive drug release. Unlike many synthetic nanocarriers, VLPs offer atomically defined structure–function relationships, allowing rational modulation of biodistribution, cellular uptake, immune recognition, and therapeutic performance. This review examines VLPs as engineered protein biomaterials for precision chemotherapy, highlighting strategies for internal cargo integration, interfacial surface modification, mechanical reinforcement, and microenvironment-triggered release. Here we discuss how physicochemical parameters govern biological interactions and translational feasibility. Clinical progress underscores both the promise and remaining challenges of scalable manufacturing and immune modulation. By integrating biomaterials design principles with translational constraints, this review outlines a framework for the rational development of clinically viable VLP-based chemotherapeutic systems.

Keywords: virus-like particles (VLPs); targeted drug delivery; chemotherapeutics; nanomedicine; precision oncology

1. Context and Unmet Needs in Cancer Treatment

Cancer remains a significant global health threat. In 2022, approximately 20 million new cases and 9.7 million cancer-related deaths were reported worldwide, underscoring the urgent need for more effective therapeutic strategies [1]. Although significant progress has been made in cancer prevention, early detection, and treatment, which has been contributing to a decline in mortality rates in many regions, the global burden of cancer is rapidly increasing [1]. This rise largely driven by population ageing and the growing prevalence of risk factors is linked to environmental and lifestyle changes [2,3].

Within this landscape, VLPs have emerged as a unique class of protein-based biomaterials for therapeutic delivery. VLPs are nanoscale assemblies formed by the self-organization of viral capsid proteins in the absence of genetic material, rendering them non-infectious while preserving the structural fidelity of native viruses offer several advantages as drug delivery systems (DDS). Their genetically encoded architecture enables precise control over particle size, symmetry, surface topology, and internal cavity volume, features that are difficult to replicate using fully synthetic

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nanocarriers. As a result, VLPs provide a modular scaffold in which structure–function relationships can be systematically tuned to influence biological performance.

VLPs traditionally known for their role vaccine development due to their intrinsic immunogenicity and ability to boost hormonal and cellular immune responses, are now gaining traction in the field of drug delivery [4]. Their biocompatibility, ability to penetrate biological barriers, innate cargo-carrying potential, and ease of surface modification make VLPs highly attractive as programmable platforms for the targeted delivery of therapeutic agents, including small molecules, chemotherapeutics, nucleic acids and proteins [5,6]. Although VLPs have been extensively reviewed as nanocarriers for a broad range of therapeutic and diagnostic cargos [4–9], their application as platforms for chemotherapeutic drug delivery has rarely been examined as a primary focus. Herein, we review recent advances in the design and functionalization of VLPs for chemotherapeutic drug delivery, highlighting their versatility, current challenges, and potential to enhance the specificity and efficacy of cancer treatments.

2. Architectural and Functional Basis

VLPs are nanoscale, protein-based assemblies that mimic the structural organization of native viruses. They are formed through the self-assembly of capsid proteins (CPs), but lack the viral genetic material, rendering them non-infectious. These nanostructures typically range from 20 to 200 nm in diameter, depending on their viral origin. Lacking genetic material and replication machinery, VLPs are non-infectious by design, yet retain intrinsic immunogenicity and strong safety profile, making them highly suitable for biomedical applications [9]. Viral structural proteins can be expressed in a variety of live or cell-free systems, after which they self-assemble into virus-like structures that can be further purified, engineered, or functionally reconstituted for specific applications. Cell-free systems are particularly attractive for VLP production as they allow tight control over reaction conditions and reduce the risk of host-cell contaminants, though they require virus-specific optimization and may not be compatible with all capsid types [10].

The structural diversity of VLPs reflects the wide range of architectures found among their viral sources. VLPs can adopt icosahedral, rod-shaped, or spherical geometries, and can be composed of one or multiple capsid proteins, forming either single- or multi-layered assemblies [11]. Some VLPs are non-enveloped, while others acquire a lipid envelope derived from the host cell membrane during the processes of assembly and budding [12]. In enveloped VLPs, such as those derived from HIV-1, Influenza and Ebola virus, viral glycoproteins embedded in the lipid membrane mediate cell entry via membrane fusion - a process governed by glycoprotein conformational changes and modulated by the lipid composition and protein–lipid interactions between the fusing membranes [12,13].

The variety of VLP shapes, sizes and surface chemistries allows for different cellular interactions, internalization pathways, biodistribution, clearance and transport within complex biological environments, such as the tumor microenvironment [14,15]. In all cases, their surface can be readily modified to incorporate targeting ligands, antigenic epitopes, or chemical linkers, enabling selective delivery to specific tissues or cells. Internally, VLPs can be loaded with a range of therapeutic payloads, including chemotherapeutic agents, nucleic acids, or imaging probes, either through covalent conjugation, encapsulation during assembly, or post-assembly diffusion [16]. Moreover, their nanoscale size allows their efficient tissue penetration and cellular uptake, while their virus-mimicking architecture can promote endosomal escape and intracellular delivery. In addition, certain VLPs naturally elude to the formation of a protein corona, a major challenge to nanoparticle delivery that can lead to nanoparticle aggregation, rapid clearance and masking of targeting ligands irrespective of administration route [17,18]. These properties make VLPs powerful candidates for programmable chemotherapeutic drug delivery systems, offering the potential to enhance treatment efficacy, reduce off-target toxicity, and overcome biological barriers that limit the performance of conventional nanocarriers.

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In the following sections, we explore the strategies for engineering VLPs as chemotherapeutic carriers, including methods for cargo loading, surface functionalization, and design considerations that influence pharmacokinetics, biodistribution, and therapeutic outcomes.

3. Engineering VLPs for Drug Delivery

3.1. Assembly-Driven Modifications and Cargo Loading

A hallmark of the utility of VLPs as delivery vehicles lies in the intrinsic connection between their self-assembly processes and functional integration. Since protein cage shape influences particle-cell interactions, biodistribution, and transport in biological environments, structural manipulation allows direct tailoring of VLP properties to supply specific therapeutic requirements [19]. Consequently, assembly-driven engineering approaches have become central to the rational design of VLPs for drug delivery applications.

The structure of VLPs is genetically encoded and therefore highly tunable. CP subunits are evolutionarily optimized to self-assemble into symmetric, hierarchically ordered shells through specific inter-subunit interactions, which define particle geometry, size, and surface topology [20]. Modulating these intrinsic CP features through single-point mutations or domain insertions provides a direct means to guide self-assembly toward alternative morphologies or to enhance capsid stability [21,22]. For example, C-terminal histidine-peptide extension introduced into chimeric hepatitis B virus core antigen (HBcAg)-VLPs conferred enhanced resistance to chemical and physical stress [23]. In the same study, a naturally occurring disulfide bond at Cys61 was identified as an additional, independent stabilizing element, contributing to the overall structural integrity of the VLPs. In another example, the introduction of cysteines through double-site mutations (L102C/P300C) at the VP1 pentamer interface of SV40 VLPs favored the formation of a homogenous population of small, T=1-like VLPs with enhanced stability, attributed to engineered disulfide bonds [24].

VLPs can self-assemble either spontaneously from CPs alone or in the presence of templates such as nucleic acids, proteins, or synthetic polymers. Template-assisted assembly provides control over particle morphology based on the characteristics of the template and offers a streamlined approach for the co-packaging of cargo. For instance, cowpea chlorotic mottle virus (CCMV)-based virus-like particles can afford spherical, icosahedral or rod-shaped structures of various sizes when assembled around different lengths of single or double-stranded DNA [25]. Similarly, tobacco mosaic virus (TMV) VLPs can attain different aspect ratios dictated by the length of the RNA template used during assembly [26]. Access to a range of geometries and sizes from the same CPs has allowed the interrogation of the impact of these properties on biodistribution, cellular uptake, and drug delivery efficiency [26–29]. Importantly, the final structure and function of a VLP is also dictated by the assembly conditions, including pH, ionic strength, temperature, and presence of divalent cations or crowding agents [30,31]. Consequently, fine-tuning these parameters allows researchers to control VLP yield, cargo loading efficiency, and structural fidelity. pH-triggered disassembly and reassembly cycles are often employed to load small-molecule drugs post-assembly, while salt concentrations can modulate capsid rigidity and porosity [32,33].

A detailed understanding of capsid assembly is therefore critical for rational VLP engineering. Experimental techniques such as cryo-electron microscopy and X-ray crystallography enable high-resolution structural characterization of individual CPs and assembled particles [34,35], while atomic force microscopy allows topographical mapping of VLPs [36,37]. Complementary methods including dynamic light scattering and size-exclusion chromatography are commonly used to assess particle size distributions and assembly homogeneity [38,39], whereas isothermal titration calorimetry and surface plasmon resonance allow interrogation of protein-protein and protein-cargo interactions [40]. Computational modeling and molecular dynamics simulations have also proven valuable for predicting assembly pathways, evaluating how different templates influence particle morphology, and identifying energetically favorable configurations [41–43].

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3.2. Surface Functionalization Strategies

VLPs offer multivalency for functionalization owing to the repetitive arrangement of their protein subunits, allowing high-density presentation of functional groups on both their external and internal surfaces. Table 1 summarizes the key functional groups commonly conjugated to VLP surfaces, including therapeutic agents, targeting ligands, cell-penetrating peptides and other supportive components, which can be installed through either genetic or chemical modifications, depending on their nature [44].

Table 1. Functional components commonly integrated into virus-like particle–based protein biomaterials for chemotherapeutic drug delivery and targeting.

Functional Group Type	Compounds	Function/Target	Application	Reference
Therapeutic Agents	Doxorubicin (DOX)	DNA intercalation; inhibits topoisomerase II	Chemotherapy	29
	Monomethyl auristatin (MMAE)	Human B lymphoma cells targeting	Chemotherapy	45
	mRNA	Protein expression	Immunotherapy, gene therapy	46
	5-fluorouracil-1-acetic acid	Binds epithelial growth factor receptor (EGFR)	Chemotherapy	47
Targeting Ligands	Folic Acid	Binds folate receptor	Targeting folate receptor–positive tumors	48
	RGD peptides	Binds integrin $\alpha v\beta 3$	Anti-angiogenesis, tumor targeting	49
	Transferrin	Binds transferrin receptor	Targeting rapidly dividing cells	50
	Aptamer (e.g., AS1411)	Targets nucleolin	Selective tumor targeting	51
	Anti-HER2 antibody	Binds HER2 receptor	Targeting HER2-positive breast cancer	52
Cell-Penetrating Peptides	TAT (HIV-derived)	Facilitates nuclear and cytosolic delivery	Intracellular delivery of drugs or genes	53
	Pep-1	Non-covalent cargo delivery	Protein or peptide delivery	54
	R9 (nona-arginine)	Promotes uptake	Enhanced internalization	55

Genetic modification pertains to the addition of foreign peptide or protein sequences into the genes encoding the capsid-forming proteins, enabling their co-expression and incorporation into the VLP during self-assembly. The new sequence can be introduced in the form of an insertion or substitution at surface-exposed loops, as well as an extension of the N- or C-termini of capsid proteins, depending on the structural tolerance of the VLP [56,57]. This method typically yields highly homogeneous products with a defined stoichiometry and orientation of the inserted functional molecule but is limited by size constraints and the biochemical properties of the insert, such as charge, hydrophobicity, and the adopted secondary structure [58,59]. Fusion of large or structurally disruptive peptides may impair VLP assembly or reduce VLP stability [58,60]. Strategies to circumvent these limitations include, for instance, the tandem core approach in hepatitis B core antigen VLPs, which enables the display of large proteins or multiple functional motifs without compromising VLP assembly and stability [61], and the use of a nonsense suppression system in MS2

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VLPs to control the density of scFv incorporation, ensuring proper folding of coat–scFv fusion proteins [62]. In most cases, structural modeling of capsid proteins can guide the rational placement of fusion sequences into permissive locations [63]. Finally, beyond the fusion of foreign proteins onto capsid proteins, single-point mutations can be introduced to reduce nonspecific interactions, by substituting binding residues with inert ones [64], or to incorporate addressable functional groups for site-specific chemical modification [65]. Genetic introduction of unnatural amino acid residues bearing bioorthogonal reaction handles, as well as the insertion of signal sequences for enzyme-mediated chemical conjugation, are highly sought-after strategies for VLP functionalization and are discussed below. The feasibility of such modifications is contingent on avoiding adverse effects on capsid assembly, stability, and any essential inbuilt functions, including receptor binding.

Chemical conjugation provides a versatile post-synthetic strategy for modifying assembled VLPs, enabling the attachment of therapeutic agents and other functional components beyond peptides and proteins. Conventional approaches exploit solvent-exposed natural amino acids on the VLP surface for selective covalent modification, most commonly lysine, cysteine, tyrosine, glutamic acid, and aspartic acid residues, which serve as reactive handles for conjugation [66]. Among these, lysine and carboxylate-containing residues are frequently targeted due to their abundance and high solvent accessibility, allowing high-density display of functional molecules. For example, Biabanikhankahdani et al. conjugated about 470 folic acid (FA) and 1600 DOX molecules to the external surface of truncated hepatitis B core antigen (tHBcAg) VLPs via primary amine and carboxylate groups, respectively, using EDC/Sulfo-NHS chemistry [67]. The resulting dual-conjugated VLPs enabled specific DOX delivery to FA receptor-overexpressing cancer cells. Alternatively, when a more precise attachment of functional groups is required, cysteines, which are rarer on VLP surfaces and often engaged in disulfide bonds, can be targeted through thiol-reactive chemistries [68,69]. In the absence of free cysteines, the genetic introduction of addressable cysteines at permissive sites is a common strategy for site-specific functionalization [68,70].

Chemical conjugation to natural amino acids is not always suitable, as nonspecific modification of abundant lysine or cysteine residues, particularly in antibodies, can lead to heterogeneous display and aggregation upon VLP functionalization [71]. To address this limitation, site-selective conjugation strategies based on genetically encoded unnatural amino acids (UAAs) have been developed, enabling the introduction of bioorthogonal reactive handles at defined positions. These engineered residues can be selectively modified using orthogonal “click” chemistries, such as azide-alkyne cycloaddition, which proceed with high specificity and efficiency under mild conditions [72,73]. For example, bacteriophage Qβ and MS2 VLPs have been functionalized via copper-catalyzed azide–alkyne cycloaddition (CuAAC) by globally incorporating azide- or alkyne-bearing methionine analogues during expression, allowing conjugation of diverse biomolecules without compromising capsid integrity [73]. While CuAAC affords stable triazole linkages, concerns over copper-induced cytotoxicity and protein oxidation have motivated the use of stabilizing ligands (e.g., TBTA or THPTA) or copper-free alternatives such as strain-promoted azide-alkyne cycloaddition [74,75].

Bacterial-derived ligation systems, such as sortase-mediated conjugation and the SpyTag/SpyCatcher system, provide comparable site-selectivity and bioorthogonality. Sortase-mediated conjugation enables site-specific attachment of functional proteins or peptides through the catalysis of a transpeptidation reaction between a C-terminal LPXTG motif engineered into the VLP and an N-terminal oligoglycine on the cargo [76]. The SpyTag/SpyCatcher system, derived from a split protein domain of Streptococcus pyogenes, enables spontaneous and irreversible covalent bond formation between a short peptide tag (SpyTag) and its protein partner (SpyCatcher). Unlike strategies based on unnatural amino acid incorporation, this genetically encoded system enables efficient, site-specific VLP functionalization under mild conditions without the need for specialized reagents or complex expression protocols, enhancing simplicity and scalability [77].

Lastly, non-covalent modification strategies, such as affinity tag interactions, provide a modular and reversible alternative to covalent conjugation while preserving the bioactivity of the cargo [78]. The trimeric decoration protein (Dec) from bacteriophage L binds P22 VLPs with high affinity and

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can serve as a scaffold for surface display without CP modification. Fusion of Dec to either the soluble region of murine CD40L or a CD47-derived "self-peptide" enabled their individual presentation on the capsid exterior, with CD47-Dec VLPs showing reduced phagocytic uptake, highlighting a strategy to prolong P22 VLP circulation time [79]. Similarly, engineered affinity tags, such as His-tag/trisNTA, have been used to decorate norovirus VLPs with peptides or fluorescent probes for targeted cellular uptake [80].

4. Current Progress in Chemotherapy Delivery

Chemotherapy remains a cornerstone of cancer treatment, yet its clinical effectiveness is often compromised by dose-limiting toxicity, inadequate specificity, and poor water solubility [81,82]. Non-selective biodistribution leads to off-target effects against healthy cells and insufficient drug accumulation at tumor sites, resulting in partial remission and the emergence of drug-resistant cell populations [81,83]. To address these limitations, recent efforts in cancer nanomedicine have focused on developing multicomponent carriers with tumor-targeting capabilities, controlled drug release, immune evasion features and other supportive components [84]. Among these, VLPs stand out as versatile nanocarriers capable of meeting the complex requirements of chemotherapeutic delivery. Herein, we highlight recent advances in the design of VLP-based carriers for chemotherapy delivery, with a focus on rational design strategies, chemically switchable systems and progress toward clinical translation.

A drug delivery system based on Flock House Virus (FHV) VLPs has been developed for targeted delivery of hydrophobic chemotherapeutic drugs [85]. FHV VLPs are icosahedral particles of about 30 nm with T=3 symmetry, assembled from 180 identical protein subunits [86]. Capsid proteins were engineered to contain a serine to lysine mutation at position 268 (S268K), located on an outer, solvent-exposed loop, for efficient attachment of the tumor-homing peptide tLyP-1 (CGNKRTR). This peptide is a linear, C-terminally truncated version of Lyp-1, a circular peptide known for its ability to specifically recognize tumor cells [87]. Peptide conjugation was carried out in two steps, using a heterobifunctional PEGylated SMCC crosslinker as the anchoring moiety, to avoid nonspecific uptake and improve biocompatibility. FHV particles exhibit dynamic behavior, a preference for hydrophobic molecules, and are stabilized by Ca2+ ions. These properties were exploited to encapsulate two hydrophobic drugs, DOX and ellipticine (EPT), via partial capsid destabilization induced by Ca2+ removal. The resulting Dox_tLyP-1_S268K and EPT_tLyP-1_S268K VLPs were stable and capable of selectively targeting MDA-MB-231 breast tumor cells in vitro, inducing apoptosis [85]. Owing to the pH-sensitive profile of FHV particles and PEGylated surface, drug release occurred in a controlled, endosome-specific manner, triggered by the acidic endosomal environment.

Another drug delivery system enabling pH-responsive cargo release was constructed from Physalis mottle virus (PhMV) VLPs [88]. These VLPs are composed of 180 identical capsid protein subunits that self-assemble into ~30 nm icosahedral particles. The uniform size, small dimensions, biocompatibility and long circulation times in vivo make these particles well-suited for drug delivery applications [89]. Furthermore, the capsid crystal structure reveals four solvent-exposed lysines on the exterior and one internal solvent-exposed cysteine, allowing site-specific modification. PhMV VLPs were loaded with the prodrug 6-maleimidocaproyl-hydrazone doxorubicin (DOX-EMCH) via thiol-maleimide conjugation to the interior addressable cysteine and PEGylated through NHS esterification of exterior lysins using methoxy-PEG N-hydroxysuccinimide (mPEG-NHS), to prevent non-specific uptake and improve biocompatibility. The inclusion of the acid-sensitive hydrazine linker EMCH allowed controlled release of DOX under acidic conditions, mimicking those of the tumor microenvironment or acidic endosomal/lysosomal compartments. DOX-PhMV-PEG particles induced cytotoxicity and DNA damage across a panel of cancer cell lines and exhibited significantly greater efficacy in vivo compared to free DOX in a breast tumor mouse model, achieving a 3.4-fold higher therapeutic efficacy.

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Certain VLPs possess inherent tumor-homing capabilities that can be directly exploited for targeted drug delivery without the need for additional modifications. One such example is the Potato Virus X (PVX) VLP, which has been harnessed for targeted delivery to Non-Hodgkin's B cell lymphomas [45]. PVX is a filamentous plant virus with demonstrated tumor-homing properties in tumor-bearing mice and preferential accumulation within B cell follicles [90]. This property has been explored for targeted delivery of the cytotoxic drug MMAE to malignant B cells, without introducing external targeting motifs. Specifically, vcMMAE was conjugated to surface-exposed cysteine residues on Potato virus X (PVX) VLPs using thiol-maleimide chemistry. The resulting PVX-vcMMAE conjugates demonstrated selective binding to CD45+ Raji B lymphoma cells and exhibited significantly enhanced cytotoxicity compared to free vcMMAE. In vivo studies in a Raji B cell lymphoma mouse model revealed that PVX-vcMMAE treatment led to tumor growth inhibition and improved survival, with no observed toxicity to normal B cells [35]. These findings underscore the potential of PVX VLPs as a platform for targeted delivery of cytotoxic agents to B cell malignancies.

A VLP-based delivery system has also been harnessed for image-guided chemotherapy, combining PET–fluorescence dual imaging and convection-enhanced delivery (CED) of epirubicin (EPI) in brain tumor therapy [91]. The base vehicle for this system is the Bacteriophage Qβ-derived VLP, whose capsid proteins were co-expressed with green fluorescent protein (GFP) to generate GFP-encapsulated Qβ virus-like particles (gVLPs). These gVLPs were surface modified with a cell penetrating peptide (CPP) to enhance cell uptake efficiency, and passively loaded with EPI under physiological conditions. DOTA moieties were conjugated for radiolabeling with 68Ga, enabling in vivo tracking via PET imaging alongside intrinsic fluorescence. CED delivery of EPI@CPP-gVLPs enabled broader intratumoral distribution and significantly reduced neurotoxicity compared to free EPI in mice brain, attributed to the stable encapsulation and CPP-controlled release of the drug. Repeated intracranial administration of EPI@CPP-gVLPs through CED infusion in tumor-bearing mice eradicated tumors without recurrence or serious brain damage, demonstrating the potential of this platform as a CED infusate for safe and effective local chemotherapy.

In another example, a papillomavirus-like particle-drug conjugate, named AU-011, has advanced to clinical evaluation for multiple tumor types. AU-011 is a drug-VLP system consisting of recombinantly expressed human papillomavirus (HPV) capsid proteins L1 and L2, conjugated to a phthalocyanine photosensitizer, IRDye 700DX, which exerts its cytotoxic effect upon photoactivation with near-infrared light (NIR) [92]. HPV capsids naturally interact with modified heparan sulfate proteoglycans (HSPGs), which have been shown to be a primary factor required for HPV entry into cells [93]. These modifications are typically restricted to basement membranes in normal tissues but become aberrantly exposed on the surface of many tumors. This tumor-tropic feature enables HPV VLPs to target a broad spectrum of tumor types without requiring additional modifications [93]. Effectively, AU-011 is currently in clinical trials for multiple types of cancer, including small choroidal melanoma (ClinicalTrials.gov: NCT06007690), bladder cancer (ClinicalTrials.gov: NCT05483868) and choroidal metastasis from breast or lung primary tumors (ClinicalTrials.gov: NCT06643884). Further, AU-011 itself may serve as an additional immunogenic catalyst within the tumor; In uveal melanoma cell lines, NIR-activated AU-011 induces calreticulin and HSP90 membrane exposure, indicative of its ability to trigger immunogenic cell death (ICD) in addition to direct cytotoxicity [94]. In another study, a single in vivo dose followed by NIR further promoted ICD hallmarks and immune activation in the tumor microenvironment, effects that were amplified by co-administration of checkpoint inhibitors, highlighting AU-011's potential in combination immunotherapy [95].

5. Challenges and Future Directions

Extensive efforts have been directed toward engineering VLPs with tunable drug release profiles, enhanced targeting, and VLP transfer across various physiological barriers. Intrinsically, VLPs possess several features that may help address key obstacles in the clinical translation of cancer nanomedicine, particularly those encountered by synthetic nanocarriers. Their diversity in structure, surface properties, and tropism provides a versatile toolbox for precision chemotherapeutic delivery.

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Beyond single-agent delivery, recent studies have highlighted the capacity of VLPs to co-deliver chemotherapeutics with synergistic payloads, such as siRNA or immunomodulatory proteins, to enhance antitumor efficacy [96,97].

Building on VLPs intrinsic advantages, incorporating material science strategies can further enhance VLP capabilities. Reinforcement of VLP architecture using synthetic polymers has emerged as a promising route to fine-tune physicochemical properties, where strategies such as surface cross-linking can increase VLP resilience under harsh conditions, including acidic pH, enzymatic degradation, and mechanical stress [98]. PEGylation remains the most widely used 'stealth' modification, reducing immunogenicity and prolonging circulation time by shielding the particle surface from opsonization [99]. Some alternative hydrophilic polymers, such as poly(2-oxazoline)s and zwitterionic coatings, are being explored to achieve comparable stealth performance while avoiding PEG-associated drawbacks [100]. Internally, polymeric cross-linkers and controlled polymerization reactions have been employed to stabilize the capsid scaffold and support higher-density small molecule cargo loading without compromising structural integrity [101,102].

Complementary to these advances, in silico tools may gain a prominent role in VLP design and translational efforts. Molecular modeling and molecular dynamics simulations enable assessment of nanoparticle structural stability under diverse conditions while providing atomistic insight into nano-bio and nano-drug interactions that are difficult to capture experimentally [103,104]. Computational approaches have already been applied to guide VLP design: for example, iterative histidine-scanning and folding free-energy calculations have been used to design pH-responsive P22 capsids that assemble and disassemble in a controlled, pH-dependent manner [104]. More broadly, AI-driven tools hold promise for advancing VLP research and development, supporting capsid structure prediction, analysis of assembly pathways, image-based particle characterization, and optimization of production and purification processes [105].

Although VLPs offer high modularity and apparent biocompatibility for drug delivery, their innate biological properties can pose significant challenges. Native tropism may drive unplanned interactions with host cell receptors, while recognition by the immune system can elicit immunogenic responses that compromise targeting specificity, circulation time and therapeutic efficacy.

A compelling case is that of cowpea mosaic virus (CPMV), a plant virus frequently used in nanomedical applications due to its stability and ease of functionalization. Despite its botanical origin, CPMV demonstrates a notable capacity to associate with mammalian cells [106]. This unexpected interaction has been linked to the presence of vimentin on the surface of certain human cells, including cancer cells and activated endothelial cells [107,108]. Vimentin, typically a cytoskeletal protein, can under some physiological and pathological conditions translocate to the cell surface, where it becomes accessible to circulating particles. The interaction between CPMV and surface-expressed vimentin facilitates uptake into non-target mammalian cells, raising concerns about off-target biodistribution. While this property can be harnessed for applications that aim to exploit surface vimentin as a biomarker, such as tumor targeting, it may compromise specificity in therapies that require strict tissue selectivity or immune stealth. To address this, researchers have explored surface engineering strategies such as PEGylation, which effectively reduces nonspecific interactions of CPMV with mammalian cells [109]. While not directly evaluated, this likely includes vimentin-mediated interactions. The extent of suppression depends on PEG density, with coverage above 80 PEG500 or 60 PEG2000 chains per particle shown to significantly minimize off-target binding [109]. Understanding and managing native tropism is thus critical to maximizing the therapeutic potential of VLPs while mitigating risks related to off-target effects.

Despite the strong preclinical performance and growing sophistication of VLP-based chemotherapeutic delivery systems, only one VLP platform has advanced into clinical trials, revealing challenges in the translation of this technology. This gap is not unique to VLPs as antitumor nanotherapeutics but reflects broader obstacles across cancer nanomedicine. Effective clinical translation requires an integrated approach that accounts for manufacturability, scalability, and regulatory constraints from the earliest stages of nanoparticle design [110,111].

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A major bottleneck is the ability to scale production in a cost-effective and reproducible manner, both for nanomedicines in general and for VLPs in particular [112]. While the biomimicry of native viral architectures confers advantages such as biocompatibility and biodegradability, these biological origins also introduce challenges related to their structural heterogeneity and complex purification from host-derived contaminants. The production of VLPs relies on complex cell culture and protein expression systems leading to comparatively high manufacturing costs [112]. Enhancing production efficiency and reducing expenses are pivotal for clinical application. As VLPs evolve toward increasingly complex, multicomponent architectures, design choices must therefore anticipate downstream constraints. The synthetic and regulatory burdens associated with nanoparticle multifunctionality have been widely discussed, suggesting that inherently versatile, minimalist designs may offer a more direct path to clinical translation [113–115]. Notably, the investigational VLP-drug conjugate AU-011 exemplifies this principle, employing a base viral vehicle with inherent tumor-tropic properties and a single conjugated chemotherapeutic agent. These considerations highlight key design parameters governing VLP biomaterial performance (Table 2).

Table 2. Design Parameters Governing Virus-Like Particle Biomaterial Performance in Chemotherapeutic Delivery.

Design Parameter	Biomaterial Feature	Controls	Design Trade-Off	References
Capsid geometry	Size and aspect ratio	Tumor penetration, circulation	Small particles enhance diffusion; elongated forms alter clearance	[15,26–29]
Capsid stability	Inter-subunit cohesion, crosslinking	Circulatory integrity, endosomal resistance	Excess rigidity may hinder intracellular release	[23,24,98,101]
Surface charge	Zeta potential	Cellular uptake, serum interaction	Positive charge increases uptake but accelerates clearance	[19,66]
Surface shielding	P[49,50,63EG or hydrophilic coatings	Immune evasion, reduced opsonization	High density may mask targeting ligands	[99,100,109]
Ligand density	Multivalent display	Receptor engagement, selectivity	Overcrowding may cause steric hindrance	[49,50,63]
Cargo loading strategy	Encapsulation or conjugation	Drug ratio, release kinetics	High loading can destabilize capsids	[32,33,67,102]
Stimuli-responsive elements	pH-, redox-, or enzyme-sensitive linkers	Site-specific drug release	Premature activation reduces efficacy	[32,88,103]
Native tropism	Intrinsic receptor affinity	Target specificity	May cause off-target accumulation	[106–109]
Manufacturing platform	Expression and purification system	Scalability, reproducibility	Complex designs increase cost	[110–112]

6. Conclusions

Programmable virus-like particles represent a powerful and adaptable platform for precision chemotherapy, offering fine control over drug loading, targeting, and release while retaining the advantageous biological features of viral architectures. Advances in capsid engineering and site-specific functionalization have enabled VLPs to overcome key limitations of conventional chemotherapeutic delivery, including poor selectivity and systemic toxicity. Nonetheless, limitations related to native tropism, immune recognition, and scalable manufacturing reinforce the need for mechanism-driven design frameworks that anticipate translational constraints. Clinical progress exemplified by AU-011 suggests that exploiting intrinsic viral properties through minimalist engineering may provide a more viable route to translation than over more complex nanocarrier designs.

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Future success in VLP-based chemotherapy will depend on integrating molecular programmability with manufacturability and regulatory feasibility, positioning VLPs as a unifying platform at the interface of nanomedicine, synthetic biology, and precision oncology.

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Abbreviations

The following abbreviations are used in this manuscript:

CCMV	Cowpea chlorotic mottle virus
CED	Convection-enhanced delivery
CP	Capsid protein
CPMV	Cowpea mosaic virus
CPP	Cell penetrating peptide
CuAAC	Copper-catalyzed azide–alkyne cycloaddition
DDS	Drug delivery system
Dec	Decoration protein
DOX	Doxorubicin
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EGFR	Epithelial growth factor receptor
EMCH	6-maleimidocaproyl-hydrazone
EPI	Epirubicin
EPT	Ellipticin
FA	Folic acid
FHV	Flock house virus
GFP	Green fluorescent protein
HBcAg	Hepatitis B virus core antigen
HER2	Human epidermal growth factor 2
HIV-1	Human immunodeficiency virus 1
HPV	Human papillomavirus
HSPG	Heparan sulfate proteoglycan
ICD	Immunogenic cell death
MMAE	Monomethyl auristatin
NHS	N-hydroxysulfosuccinimide
NIR	Near-infrared light
PEG	Polyethylene glycol
PhMV	Physalis mottle virus
PVX	Potato virus X
RGD	Arginylglycylaspartic acid
scFv	Single-chain variable fragment
siRNA	Small interfering RNA
SV40	Simian virus 40
TMV	Tobacco mosaic virus

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UAA Unnatural amino acid
VLP Virus-like particle

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