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REVIEW

Concept of 2D van der Waals Nanohybrids for Key Biomedical Applications

N Sanoj Rejinold[1,2], Jin-Ho Choy[1,3]

[1]Intelligent Nanohybrid Materials Laboratory (INML), Department of Chemistry, College of Science and Technology, Dankook University, Cheonan, 31116, Republic of Korea; [2]International Convergence Technology Cooperation Leading Center (ICTCLC), Global Chemical Convergence Research Institute, Dankook University, Cheonan, 31116, Republic of Korea; [3]Division of Natural Sciences, The National Academy of Sciences, Seoul, 06579, Republic of Korea

Correspondence: Jin-Ho Choy, Email jhchoy@dankook.ac.kr

Abstract: The past decade has witnessed a fundamental shift in 2D nanomaterials, from isolated single-component sheets to vdW nanohybrids, architected as stacked, stitched, or surface-engineered assemblies of chemically distinct layers. Enabled by weak interlayer forces, these hybrids permit modular integration of photonic, catalytic, electronic, and bioactive functions without lattice matching or harsh chemistries. In biomedicine, this modularity is transformative: one layer can absorb Near Infrared, NIR light for photothermal or photodynamic therapy, another can intercalate and release drugs or nucleic acids, a third can modulate redox biology through ROS scavenging or nanozyme activity, while polymeric or biomimetic coatings provide immune evasion, targeting, or biodegradability. Compared with isotropic nanoparticles, 2D vdW interfaces offer maximal surface area, multivalent binding, anisotropic ion/electron transport, tissue-compliant mechanics, and engineerable interlayer galleries for controlled, stimulus-responsive release. Crucially, vdW stacking preserves the intrinsic properties of each layer while enabling emergent synergistic behaviors including photothermal–photodynamic coupling, catalytic–photonic amplification, mechanobiology-driven responsiveness, and staged therapeutic logic. Together, these attributes position vdW nanohybrids as a powerful and versatile class of materials poised to redefine therapeutic, diagnostic, regenerative, and bioelectronic frontiers in next-generation nanomedicine.

Keywords: Van Der Waals nanohybrids, 2D materials, mxene, layered double hydroxides, LDH, biomedical applications

Introduction

Over the past decade, the field of two-dimensional (2D) materials[1–20] has undergone a profound transformation from simple single-component nanosheets to complex vdW nanohybrids, which are architecturally assembled through weak interlayer forces. The origins of this hybridization concept can be traced to landmark studies in the late 1990s, when the term "nanohybrid" was coined to describe inorganic–organic layered systems featuring engineered interfaces and tunable functionalities.[21–23] This early vision of combining disparate materials at the nanoscale presaged today's vdW design paradigm, in which multiple 2D layers are coupled through controlled non-covalent interactions. [24–26]

This evolution has liberated materials design from the rigid constraints of lattice matching and harsh synthesis, allowing diverse layers to coexist and interact in a modular fashion. Within these heterostructures, each layer preserves its intrinsic optical, electronic, or catalytic properties while simultaneously contributing to emergent collective behaviors that transcend the sum of their parts.[27]

In biomedicine, this paradigm shift holds exceptional promise. The modularity of vdW nanohybrids enables precise functional integration: one layer can harvest light for photothermal or photodynamic therapy,[28] another can load and release drugs, nucleic acids, or imaging agents, while yet another can act as a reactive oxygen species (ROS) scavenger or Fenton-like catalyst for redox regulation. Polymeric or biomolecular coatings further endow these systems with stealth characteristics, active targeting capabilities, and controllable biodegradability, transforming synthetic assemblies into biologically intelligent constructs.[29]

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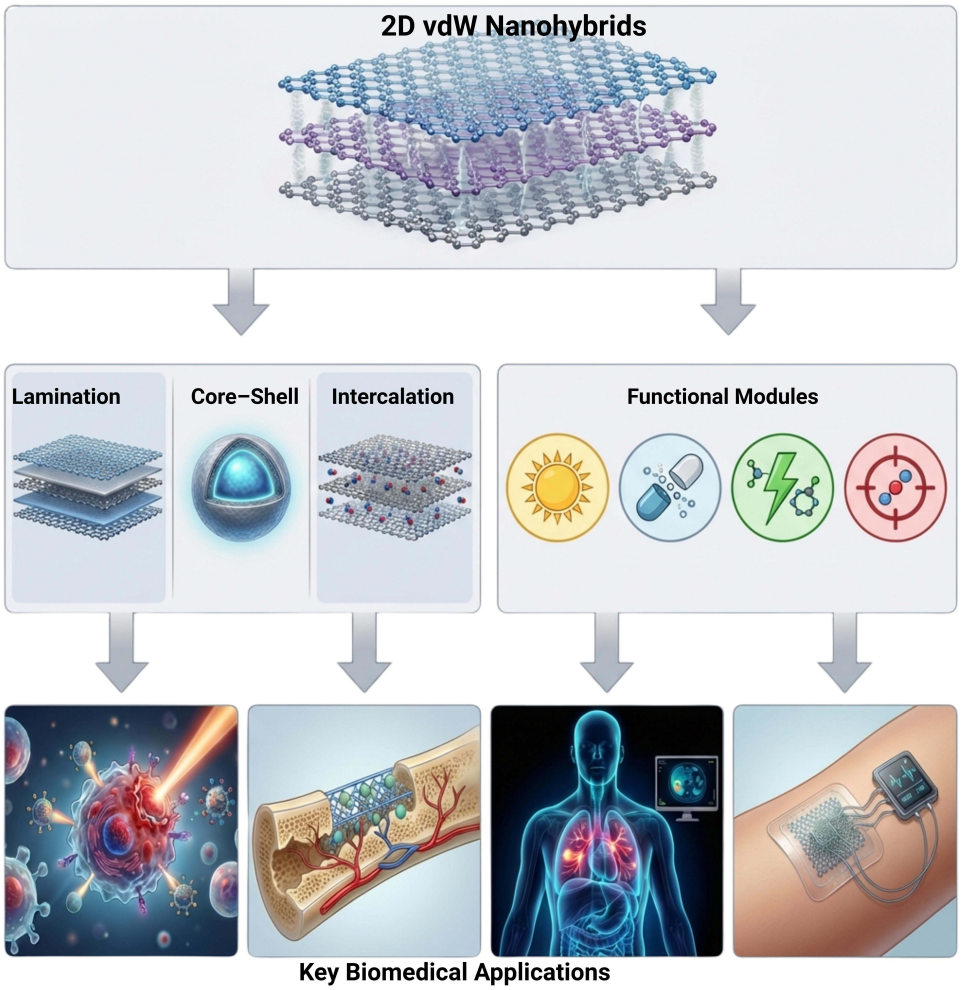
Graphical Abstract



Unlike isotropic nanoparticles, ultrathin 2D interfaces present a unique combination of physicochemical advantages: their high specific surface area allows dense molecular loading and multivalent interactions; their anisotropic structure facilitates directional ion and electron transport; their mechanical softness mimics native tissues; and their tunable interlayer spacing provides a dynamic platform for intercalation-controlled or stimuli-responsive release.[30] As a result, vdW nanohybrids are not passive carriers but active participants in the therapeutic process, interacting with biological systems through programmable energy transfer, charge mediation, and molecular recognition.[31]

The interplay among layers within vdW assemblies gives rise to emergent synergistic behaviors—synergistic photothermal–photodynamic effects, catalytic–photonic coupling, and staged release mechanisms that mimic biological logic. Such programmable functionality marks a critical step toward bioinspired design, where energy conversion, redox regulation, and signal modulation occur in concert at the nanoscale. vdW nanohybrids thus represent a new frontier in the creation of adaptive, multifunctional biointerfaces capable of responding intelligently to complex physiological environments.

Despite these advances, the field remains in a formative stage. Research across materials science, photonics, catalysis, and nanomedicine has produced remarkable findings, yet comprehensive frameworks linking molecular design, interfacial mechanisms, and biomedical translation are still lacking.[32] Persistent challenges such as achieving structural

stability under physiological conditions, ensuring biodegradability and safety, and scaling production without compromising performance must be addressed before clinical integration becomes a reality. However, a successful clinical translation requires compliance with regulatory frameworks such as those established by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), including rigorous evaluation of safety, pharmacokinetics, and long-term biocompatibility. Despite promising preclinical findings, many vdW nanomaterials remain at an early stage of biomedical investigation.

This review seeks to synthesize the growing body of knowledge surrounding vdW nanohybrids in biomedicine, elucidating their structural design principles, functional mechanisms, and emergent interlayer dynamics. We discuss how vdW stacking, interfacial coupling, and surface modification can be strategically tuned to achieve multifunctional synergy—spanning photothermal-photodynamic cooperation, redox catalysis, gene and drug delivery, and diagnostic imaging. By bridging the divide between materials chemistry and biomedical engineering, this review aims to chart a conceptual roadmap for the rational design of vdW nanohybrids. More than a catalog of existing technologies, it provides a vision for how these atomically thin architectures may redefine nanoscale medicine, transforming inert carriers into intelligent, self-regulating, and adaptive therapeutic platforms capable of precise, integrated biological intervention.

Naturally Occurring 2D Van Der Waals Hybrids

Naturally occurring layered minerals have recently re-emerged as an important but underexplored source of 2D vdW materials. Beyond the classic examples of graphite and molybdenite, several complex sulfosalt minerals found in nature already exist as inherent vdW heterostructures, essentially "natural 2D hybrids" composed of alternating chemically and structurally distinct layers. Notably, minerals such as franckeite, cylindrite, and cannizzarite possess intrinsic mixed-layer architectures (eg, SnS_2-like and PbS-like layers in franckeite) that mirror the artificial van der Waals superlattices created through modern material assembly techniques (Figure 1). These natural vdW hybrids exhibit emergent properties arising from their internal heterostructuring, including p-type semiconducting behavior, strong anisotropy, and even magnetic interactions, demonstrating that hybridized 2D architectures are not exclusively synthetic constructs but also occur spontaneously in geological environments. This perspective highlights that the conceptual foundation of vdW nanohybrids has deep natural precedents and that studying such minerals can inspire new design rules for engineered 2D hybrid materials.[33]

Taxonomy of 2D Building Blocks for Van Der Waals Nanohybrids

The foundation of vdW nanohybrids lies in the vast and chemically diverse family of 2D materials, each offering unique physicochemical attributes that can be harnessed for biomedical design. These building blocks can be broadly categorized according to their composition, bonding characteristics, and functional tunability, which collectively dictate their interactions with biological systems. The taxonomy of biomedical 2D materials spans inorganic, organic, and hybrid classes, each contributing distinct advantages toward multifunctional nanohybrids.

Inorganic 2D Materials

This category encompasses transition metal dichalcogenides (TMDs),[34–44] metal oxides,[45–55] metal hydroxides,[56–61] and layered double hydroxides (LDHs),[62] all of which exhibit tunable electronic and catalytic properties. TMDs (eg, MoS_2, WS_2, TiS_2) possess high photothermal conversion efficiency and strong near-infrared absorption, making them valuable for photothermal and photodynamic therapies.[28] Their semiconducting nature also supports charge transfer processes essential for catalytic and sensing applications. Metal oxides and hydroxides (eg, MnO_2, TiO_2, ZnO, Mg(Al)–LDH) exhibit excellent biocompatibility and can modulate oxidative stress by scavenging or generating reactive oxygen species (ROS).[63] LDHs, in particular, serve as ion-exchangeable hosts for drug, gene, or biomolecule intercalation, enabling pH-responsive and sustained release behavior.[62,64–79] 2D metals and carbides (MXenes,[80] eg, Ti_3C_2Tx[81]) represent a new generation of conductive materials with large surface charge densities and rich surface terminations (–OH, –O, –F), which can be exploited for electronic interfacing, photothermal therapy, and biosensing. The key attributes of each subclass are summarized in Table 1.

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Figure 1 Overview of Naturally Occurring vdW Layered Minerals and Exfoliated 2D Nanosheets (Panels (**a**–**i**)). (**a**) Elemental van der Waals minerals. Three-dimensional crystal structures, mineral photographs, and optical microscopy images of exfoliated flakes of graphite, native antimony, native bismuth, native selenium, and native tellurium. Single-layer and few-layer graphene flakes obtained from natural graphite are also shown; (**b**) Sulfide van der Waals minerals. Crystal structures, bulk mineral images, and exfoliated nanosheets of naturally occurring molybdenite (2H and 3R polytypes), tungstenite (2H-WS_2), orpiment (As_2S_3), anorpiment (As_2S_3 dimorph), stibnite (Sb_2S_3), and getchellite ($AsSbS_3$); (**c**) Sulfosalt van der Waals minerals (natural vdW heterostructures). Three-dimensional structures, mineral samples, and exfoliated flakes of teallite ($PbSnS_2$), franckeite ($Pb_5Sn_3Sb_2S_{14}$), cylindrite ($Pb_3Sn_4FeSb_2S_{14}$), and cannizzarite ($Pb_4Bi_6S_{13}$). These minerals consist of alternating chemically distinct layers, representing naturally formed vdW heterostructures; (**d**) Oxide van der Waals minerals. Crystal structures and mineral images of valentinite (Sb_2O_3) and birnessite (Mn-oxide), with corresponding exfoliated flakes including TEM imaging of birnessite nanosheets; (**e**) Nesosilicate van der Waals minerals. Structure, bulk specimen, and exfoliated flake of kyanite (Al_2SiO_5); (**f**) Phyllosilicate clay minerals. Crystal structures, bulk samples, and exfoliated nanosheets of talc and vermiculite, including thermally expanded vermiculite used for facile exfoliation; (**g**) Phyllosilicate mica minerals. Crystal structures, natural specimens, and exfoliated flakes of muscovite, biotite, lepidolite, and phlogopite; (**h**) Phyllosilicate chlorite minerals. Crystal structure, mineral specimen, and exfoliated flake of clinochlore and (**i**) Phosphate and carbonate van der Waals minerals. Crystal structures, natural specimens, and exfoliated nanosheets of vivianite ($Fe_3(PO_4)_2 \cdot 8H_2O$) and malachite ($Cu_2CO_3(OH)_2$). This composite figure is adapted from "Naturally occurring van der Waals materials", npj 2D Materials and Applications (2020), published under the Creative Commons Attribution 4.0 International License (CC BY 4.0).[33]

Table 1 Unified Overview of 2D Inorganic Nanomaterials and Their Key Attributes

Subtype of Polymer–vdW Hybrid	Representative Polymers/Components	Structural Features	Key Functional Advantages
Polymer–TMD Hybrids	PEG, PVP, PLGA, PEI coated on MoS_2, WS_2,[82,83]	Polymer chains anchored via electrostatic or vdW interactions on 2D TMD basal planes[84] Typical photothermal conversion efficiency: **35–55%**	• Increased dispersibility and stability[85] • Enhanced biocompatibility[86] • Improved photothermal conversion efficiency[87] • Tunable drug loading on polymer surface[88]
Polymer–Metal Oxide Hybrids	PEG, PVA, chitosan on TiO_2,[89] MnO_2 nanosheets[90]	Thin polymer layers interfacing with metal oxide planes via vdW forces and hydrogen bonding[91] Typical efficiency: **20–40%**	• ROS-regulating activity with reduced cytotoxicity[92] • Better physiological stability[93] • Enhanced targeting through polymer functionalization[86]
Polymer–Metal Hydroxide Hybrids	GelMA, alginate, PVP on $Mg(OH)_2$,[94] $Zn(OH)_2$ nanosheets	Polymer coating stabilizes hydroxide lamellae and prevents dissolution[95] Typical photothermal / catalytic efficiency: **15–35%**	• Boosted antioxidant/ROS-interactive behavior[96] • Low toxicity and improved cellular interaction[97] • pH-responsive degradation[96]
Polymer–LDH Hybrids	PAA, PEG, PVP, chitosan with Mg–Al–LDH,[98] Zn–Al–LDH[99]	Polymer intercalation or surface adsorption on LDH galleries[99] Typical photothermal efficiency: 20–45%	• High drug/gene loading capacity[100] • Sustained, pH-controlled release[100] • Improved colloidal stability and ispersibility[100]
Polymer–MXene Hybrids	PEG, PNIPAM, PVA, polydopamine with Ti_3C_2Tx[101]	Polymer chains adhere to MXene surfaces terminated with –OH/–O/–F groups[101] Typical photothermal conversion efficiency: **40–70%**	• Suppressed oxidation and improved stability[97] • Enhanced conductivity and photothermal performance[102] • Increased biocompatibility and targeting functionality[103]
Polymer–2D Metal Nanosheet Hybrids	PEG, PLGA, dextran with 2D Au, Ag nanosheets[91]	Polymer corona assembled through vdW interaction with metal surfaces[97] Typical efficiency: **45–80%**	• Controlled biodistribution[97] • Improved stealth properties (reduced opsonization)[97] • Tunable plasmonic/photothermal response[104]
Polymer–Graphene/GO/ rGO Hybrids	PEG, chitosan, PLGA, PVP with GO/rGO[105]	Polymer adsorption on aromatic basal planes via π–π and vdW interactions[106] Typical photothermal conversion efficiency: **30–55%**	• Enhanced water dispersibility[105] • High drug capacity through π–π stacking[107] • Strong photothermal effect with reduced toxicity[108]

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Carbon-Based 2D Materials

Graphene and its derivatives are prototypical 2D vdW materials because their atomic layers are held together solely by weak vdW forces without interlayer covalent bonding.[109–112] This structural feature enables easy exfoliation into monolayers, exposure of a dangling-bond–free basal plane, and surface-dominated physicochemical behavior, all of which are foundational for their biomedical utility. Within this vdW family, graphene oxide, reduced graphene oxide (rGO), and graphdiyne offer distinct advantages. The sp^2-hybridized carbon framework of graphene provides exceptional electronic conductivity, mechanical flexibility, and broadband optical absorbance. Graphene oxide can be richly functionalized with polymers, peptides, ions, or drugs, yielding highly tunable therapeutic and diagnostic platforms. Graphdiyne, containing both sp and sp^2 carbon linkages, introduces intrinsic porosity, ordered π-conjugation, and superior charge-transfer capacity—features that enhance molecular adsorption, photodynamic reactivity, and bioelectrocatalysis in advanced biomedical applications.

Polymeric and Biomolecular 2D Sheets

Polymeric and biomolecular 2D sheets can be engineered through bottom-up polymerization, interfacial assembly, or exfoliation of layered precursors, producing ultrathin lamellae whose layers are held together primarily by noncovalent, vdW interactions. In many cases, the sheets form spontaneously at liquid–liquid, air–water, or solid–liquid interfaces, where polymer chains or biomolecules align laterally and assemble into planar architectures only a few nanometers thick. Because these structures lack perpendicular covalent cross-links, their layers stack through vdW forces, hydrophobic attraction, hydrogen bonding, and π–π interactions, mirroring the behavior of classical inorganic vdW materials such as graphene or LDHs.

This vdW-type lamellar organization is what makes polymeric and biomolecular sheets "2D vdW materials":

- Their surfaces are atomically smooth and free of dangling bonds,
- The interlayer adhesion is weak, enabling exfoliation or restacking, and
- Their properties are dominated by interface chemistry rather than bulk volume.

Emerging classes of 2D organic frameworks including covalent organic frameworks (COFs),[113–124] 2D polymers, and biopolymer nanosheets (eg, chitosan, gelatin, silk fibroin) are produced using interfacial polymerization, freeze-shearing, mechanical delamination, or electrostatic self-assembly. These approaches yield flexible, biodegradable sheets with ordered pores and tunable hydrophilicity, enabling high drug-loading capacities and selective molecular recognition. When incorporated into vdW stacks, these 2D organic layers contribute mechanical softness, biodegradability, and programmable interactions with cells and tissues.

Surface grafting with targeting ligands, peptides, or growth factors further transforms these sheets into precision delivery platforms, capable of tissue-specific targeting and immunomodulation. By integrating these organic 2D layers with inorganic nanosheets (graphene, LDH, TMDs), polymer–vdW hybrids combine structural anisotropy with biomolecular functionality, resulting in exceptional stability, tunable release kinetics, enhanced photothermal/ROS performance, and disease-selective therapeutic activation (Table 2). [125] From a translational perspective, the scalability of polymeric and biomolecular 2D sheets remains an important consideration. Several fabrication strategies such as interfacial polymerization at liquid–liquid interfaces, freeze-shearing, and roll-to-roll film formation, have demonstrated potential for producing large-area ultrathin sheets with controlled thickness and morphology.[126] However, challenges remain in maintaining structural uniformity, controlling defect density, and ensuring reproducibility during scale-up. The economic feasibility of large-scale production is also influenced by precursor availability, solvent recycling, and purification requirements. Addressing these issues will be essential for translating polymeric vdW nanosheets from laboratory-scale synthesis to industrial and biomedical applications.

Table 2 Overview of representative 2D inorganic vdW nanomaterials and their functional characteristics as building blocks for hybrid nanoplatforms

Subtype of 2D Inorganic Nanomaterials	Representative Examples	Core Functional Attributes
2D Transition Metal Dichalcogenides (TMDs)	MoS_2, WS_2, TiS_2	• Strong photothermal/photodynamic activity[127] • High NIR absorption[128] • Semiconducting layers facilitating charge transfer
2D Metal Oxides	MnO_2 (δ-MnO_2,[129] birnessite-type layered MnO_2) TiO_2 (anatase/rutile TiO_2 nanosheets)[130] ZnO (ZnO nanosheets)[131]	• Redox-active surfaces for ROS modulation[132] • High biocompatibility[133] • Catalytic activity for therapeutic and sensing applications[134]
2D Metal Hydroxides	Mg(Al)–hydroxide,[135] Zn(Al)–hydroxide[136]	• Layered lamellae capable of ROS interaction[96] • Biocompatible and surface-active[137] • Useful for detoxification and antioxidant regulation[138]
2D Layered Double Hydroxides (LDHs)	Mg(Al)–LDH,[139] Zinc Basic Salts,[140] Calumite (In hydrocalumite, the divalent cations are exclusively Ca^{2+})	• Ion-exchanging galleries for drug/gene loading[140] • pH-responsive and sustained release[141] • Stable inorganic hosts for biomedical delivery[68]
2D Metals & MXenes	Ti_3C_2Tx,[142] Nb_2C,[143] Mo_2TiC_2[143]	• Highly conductive surfaces[143] • Rich terminations (–OH, –O, –F) for functionalization[144] • Strong photothermal effects and biosensing capability[144]

Coordination and Metal–Organic Frameworks-Based 2D Nanosheets

2D metal–organic frameworks (MOFs) and porphyrin-based nanosheets behave as vdW materials because their ultrathin layers are assembled through weak, noncovalent interactions, primarily vdW forces, π–π stacking, and coordination-driven planar packing, rather than through continuous 3D covalent networks.[145–156] In their 2D form, these structures consist of metal centers bridged by organic linkers arranged in a single molecular plane, producing sheets only a few nanometers thick that can be exfoliated, restacked, or integrated into heterostructures much like graphene or LDH nanosheets.

This vdW-layered architecture provides exceptional tunability: metal nodes impart catalytic or redox activity, while organic linkers (including porphyrins, phthalocyanines, or polyaromatic units) define optical absorption, charge-transfer behavior, and chemical specificity. As a result, 2D MOFs and porphyrinic nanosheets can function as potent photosensitizers for photodynamic therapy, enzyme mimics for ROS regulation, or charge mediators in photo-electrocatalysis.

Their structural modularity also enables vdW stacking with other 2D materials such as TMDs, LDHs, graphene, or polymeric nanosheets, forming hybrid architectures with cooperative properties. These vdW-integrated systems often exhibit enhanced photothermal conversion, accelerated ROS generation, improved charge separation, and synergistic catalytic behavior, making them powerful platforms for cancer therapy, antimicrobial applications, and redox-based biomedical interventions.

Similarly, 2D porous coordination polymers (PCPs) represent a class of crystalline materials in which metal nodes and organic ligands assemble into atomically thin layers. While strong coordination bonds define the in-plane network, the stacked layers are held together primarily by weak vdW forces, hydrogen bonding, or π–π interactions. This anisotropic architecture, characterized by strong bonding within the plane and weak vdW adhesion between adjacent layersenables 2D PCPs to behave as true vdW materials, allowing exfoliation into monolayers and facile integration into vdW heterostructures.

PCPs exhibit unique features such as flexible frameworks, abundant accessible active sites, and high surface areas. However, controllable, scalable, and cost-effective synthesis of high-quality 2D PCP nanosheets remains a major challenge for practical applications. Conventional solvothermal or interfacial synthesis methods often yield limited quantities and require careful control of precursor concentration, temperature gradients, and solvent systems to maintain structural uniformity. Recent advances in synthesis strategies, including interfacial coordination polymerization, liquid-phase exfoliation, microfluidic-assisted growth, and continuous-flow synthesis, are beginning to enable larger-area production and improved reproducibility of ultrathin PCP sheets. Nevertheless, further efforts are required to optimize

precursor cost, solvent recycling, and manufacturing reproducibility to facilitate industrial-scale production. In addition, scalable synthesis protocols must ultimately align with regulatory and good manufacturing practice (GMP) standards if these materials are to transition from laboratory research to biomedical or technological applications.[157]

Bioinspired and Hybrid Systems

Bioinspired 2D sheets extend the vdW design space beyond purely synthetic materials by introducing interfaces that naturally couple inorganic stability with biological adaptability. Phospholipid-derived layers, protein nanosheets, and clay–biopolymer composites represent soft 2D assemblies whose lamellar organization is stabilized by noncovalent forces, including vdW, hydrogen bonding, and electrostatic interactions, similar to classical vdW materials. Layered silicates and clays such as montmorillonite, hectorite, and laponite provide high cation-exchange capacity, tunable hydration behavior, and excellent biocompatibility. Their abundance, low toxicity, and ability to intercalate therapeutics make them powerful platforms for drug delivery, wound repair, and regenerative medicine.

When integrated with biomolecules (eg, peptides, polysaccharides, growth factors), these layered systems self-assemble into hierarchical, Extra Cellular Matrix (ECM) mimetic architectures that recapitulate native cell–matrix adhesion, viscoelasticity, and signaling. Such hybrid 2D constructs behave as vdW nanointerfaces, enabling modular stacking with synthetic 2D materials (graphene, LDH, TMDs, MXenes) to engineer multi-functional heterostructures.

Taken together, these bioinspired and hybrid 2D building blocks form an expanded "periodic table" for vdW nanohybrids. By rationally stacking layers with orthogonal functions photothermal heating, ROS regulation, catalytic activity, immunomodulation, or mechanoresponsive behavior researchers can generate emergent properties that surpass the capabilities of any single component. This layered design logic enables the creation of adaptive, modular, and bioresponsive vdW platforms capable of seamless integration into complex biological environments.

Assembly Principles and Surface Bioengineering

The defining feature of vdW nanohybrids lies in their modular assembly the ability to stack dissimilar 2D layers through weak interfacial interactions while preserving the intrinsic integrity of each component. This assembly paradigm offers unprecedented control over composition, sequence, and interlayer coupling strength, leading to hybrid architectures where functionalities can be spatially segregated yet electronically or chemically coupled. The principles that govern this assembly stem from a delicate balance between thermodynamic compatibility, surface energy minimization, and electrostatic or hydrogen-bonding stabilization at the nanoscale interface. [158]

At the heart of vdW assembly is the interlayer interaction landscape, primarily governed by noncovalent forces such as vdW attraction, π–π stacking, hydrogen bonding, and electrostatic interactions.[159] To better illustrate how different intermolecular forces govern each stacking architecture, an interaction matrix is presented in **Table 3**, summarizing the dominant bonding types across laminar, core–shell, and intercalated vdW hybrids. Unlike covalent composites, where interface formation often disrupts crystal symmetry or chemical identity, vdW heterostructures can retain their pristine 2D lattice structures under idealized or ex vivo conditions, allowing interlayer coupling without strict lattice matching. In biological environments, however, these lattice structures may not remain strictly static. When vdW nanomaterials are exposed to physiological fluids, dynamic structural and surface transformations can occur due to interactions with proteins, lipids, ions, and varying pH conditions. Processes such as protein corona formation, oxidative surface modification, ion exchange, and partial lattice perturbation may influence the stability and functionality of the assembled layers. These structural dynamics can alter interlayer spacing, surface charge, catalytic activity, and degradation behavior, ultimately affecting biodistribution, cellular uptake, and long-term safety profiles. Consequently, although vdW heterostructures can preserve their crystalline architecture under controlled conditions, their behavior in biological systems should be considered dynamic rather than perfectly preserved. This non-destructive integration enables modular stacking of materials with vastly different chemistries, metallic, semiconducting, dielectric, or organic, into coherent, multi-functional ensembles.[159] The resulting heterointerfaces act as tunable energy or charge-transfer junctions, where photonic, catalytic, or electrochemical phenomena can be tailored by adjusting layer sequence, thickness, or interlayer distance.

Table 3 Mapping of Major Bonding Interactions Across vdW Stacking Modes

Bonding Type	Lamination	Core–Shell	Intercalation
Van Der Waals	✓✓✓	✓✓	✓
π–π stacking	✓✓	–	–
Electrostatic	✓	✓✓✓	✓✓✓
Hydrogen bonding	✓	✓✓✓	✓
Coordination	–	✓✓✓	✓✓
Hydrophobic	–	✓✓	✓
Host–guest confinement	–	–	✓✓✓

Notes: ✓ indicates minor contribution; ✓✓ indicates moderate contribution; ✓✓✓ indicates dominant contribution; – indicates negligible or no significant contribution. The matrix summarizes how seven key intermolecular forces—van der Waals attraction, π–π stacking, electrostatic interactions, hydrogen bonding, coordination bonding, hydrophobic interactions, and host–guest confinement—contribute differentially to three vdW stacking architectures. Face-to-face lamination relies primarily on vdW and π–π interactions for planar adhesion and charge delocalization, core–shell systems employ strong electrostatic, hydrogen-bonding, and coordination forces for radial stabilization, and intercalation-expanded galleries are dominated by electrostatic coupling and host–guest confinement that regulate basal spacing expansion and stimuli-responsive cargo release.

In biomedical systems, this assembly freedom translates directly into functional adaptability. For instance, hydrophilic layers such as layered double hydroxides or metal oxides can act as drug-intercalation reservoirs,[160] while hydrophobic graphene or MoS_2 layers serve as photothermal transducers. The vdW gap between these layers can be engineered to mediate molecular diffusion, electrostatic retention, or redox-driven release, introducing spatiotemporal control over therapeutic action. By fine-tuning interlayer charge density and dielectric environment, it is possible to modulate the kinetics of drug release or the efficiency of photothermal-photodynamic synergy, enabling programmable therapeutic logic within a single construct.

Surface bioengineering plays an equally critical role in bridging synthetic precision with biological compatibility. Bare 2D materials often suffer from rapid opsonization, aggregation, or immune clearance in physiological media. To mitigate these issues, surface modification strategies have evolved from simple polymer coatings to multifunctional biointerfaces capable of engaging with biological systems in a dynamic and responsive manner.[161] Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and zwitterionic polymers are routinely employed to enhance colloidal stability and prolong circulation by suppressing protein adsorption.[162] Meanwhile, surface conjugation with targeting ligands—such as folic acid, RGD peptides, or antibodies endows vdW nanohybrids with molecular recognition capabilities that facilitate selective accumulation in tumor or inflamed tissues via receptor-mediated endocytosis.[163]

Beyond passive stealth or targeting, next-generation bioengineering approaches integrate stimuli-responsive and biomimetic elements directly onto vdW surfaces. For example, cell membrane cloaking can replicate the antigenic profile of leukocytes or cancer cells, allowing immune evasion and homotypic targeting. Similarly, the incorporation of pH-, redox-, or enzyme-sensitive linkers enables vdW nanohybrids to respond to microenvironmental cues such as tumor acidity or oxidative stress, triggering site-specific disassembly or release. Hydrophilic polymer brushes, peptide amphiphiles, and lipid monolayers can be employed to modulate protein corona formation, control cell–material interactions, and direct intracellular trafficking.[164]

The interplay between interlayer assembly and surface functionalization ultimately dictates the physicochemical identity and biological fate of vdW nanohybrids. Interfaces can be tuned to enhance charge transfer for phototherapy, to promote catalytic ROS generation for oxidative regulation, or to suppress nonspecific adsorption for improved biocompatibility. Thus, rational surface engineering guided by both materials science and biological insight enables vdW nanohybrids to evolve from passive nanostructures into intelligent, responsive bioarchitectures.

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In essence, the assembly principles of vdW nanohybrids offer a flexible framework for integrating heterogeneous functionalities, while surface bioengineering ensures that these sophisticated materials can operate harmoniously within the dynamic and complex milieu of living systems. Together, these two pillars define the path toward clinically translatable, adaptive nanoplatforms that combine structural precision, functional modularity, and biological sophistication.

vdW Stacking Modes

The assembly of vdW nanohybrids can be orchestrated through diverse stacking modes that dictate their structural hierarchy and functional integration. Each stacking configuration, whether laminar, core— shell, or intercalation-expanded, offers a unique framework for coupling photonic, catalytic, and therapeutic processes within a single construct. By tailoring the geometry and sequence of 2D interfaces, it becomes possible to engineer nanosystems that operate through synergistic physical and chemical interactions, amplifying their performance in biomedical contexts.

Face-to-face lamination represents the most classical vdW stacking strategy, where two or more 2D sheets are brought into intimate contact through vdW attraction, π–π stacking, or electrostatic complementarity.[165] This configuration, exemplified by assemblies such as GO//MoS_2[166] or MXene//LDH,[167] creates bidirectional charge and energy transfer pathways across the heterointerface. The resulting junction can potentially facilitate photothermal–catalytic synergy, wherein photothermal layers such as graphene oxide or MXene absorb and convert light energy, while catalytic layers like LDH or MoS_2 utilize this energy to drive redox reactions or ROS modulation. Such face-to-face architectures maintain minimal lattice strain and preserve each layer's intrinsic crystallinity, allowing reversible delamination and reassembly under physiological conditions an advantageous feature for responsive drug release or degradable biomedical devices.

Beyond planar stacking, core–shell analogues extend vdW principles into three-dimensional configurations, typically constructed via layer-by-layer deposition on 2D cores.[168] The magnetic LDH system intercalated with polydopamine-modified carbon dots represents a prototypical core–shell vdW nanohybrid. In this architecture, a magnetic core provides the central functional platform, while LDH sheets form an inorganic shell that offers positive surface charge, ion-exchange capability, and structural rigidity. The outer layer of polydopamine-modified carbon dots adheres to the LDH surface through a cooperative network of electrostatic attraction, hydrogen bonding, catechol–metal coordination, and weak vdW forces. Together, these interactions generate a radially organized, multilayered hybrid in which optical, catalytic, and magnetic functionalities are spatially integrated without disturbing the crystallinity of the individual components. This makes the system an ideal example of core–shell vdW stacking for biosensing and spectrofluorometric applications.[125]

A third and particularly versatile mode involves intercalation-expanded galleries, in which guest molecules are inserted between the layers of host materials such as LDHs, 2D-MOFs, or clay nanosheets. This intercalation process expands the basal spacing of the host lattice, generating nanoscopic compartments that can accommodate a wide range of therapeutic or genetic cargos, including small-molecule drugs, siRNA, and plasmid DNA.[69,70,136,141,169–172] The release of these intercalated species can be finely controlled by pH variations, ion exchange, or redox stimuli, making such architectures inherently self-regulating. Moreover, intercalation expands the host's electronic and ionic conductivity, enabling simultaneous therapeutic release and catalytic activation under physiological conditions. The ordered, layer-by-layer geometry also ensures molecular uniformity and reproducibility; key factors for clinical translation.

Together, these vdW stacking modes: laminar, core–shell, and intercalation-expanded form the structural and functional foundation of hybrid 2D biomedical systems. Through judicious design, researchers can manipulate interfacial proximity, diffusion pathways, and energy flow to achieve emergent phenomena such as photothermal–photodynamic synergy, catalytic–photonic coupling, or ion-responsive drug release. The ability to rationally select and combine stacking motifs thus represents a powerful tool in constructing next-generation adaptive nanohybrids, capable of integrating diagnosis, therapy, and regulation within a single intelligent platform.

Non-Covalent and Covalent Strategies

The stability, functionality, and biocompatibility of vdW nanohybrids are largely determined by how their surfaces and interfaces are engineered. The integration of functional molecules, polymers, or biomolecules onto 2D substrates can be achieved through two complementary approaches: non-covalent and covalent strategies. Each offers distinct advantages non-covalent methods preserve the pristine lattice and electronic properties of the material, while covalent modifications provide durable and chemically specific anchoring for biofunctional components. The interplay between these two chemistries underpins the versatility and adaptability of vdW systems in biomedical applications.

To contextualize the chemical toolbox available for vdW interface engineering, Table 4 summarizes the principal non-covalent and covalent strategies used to functionalize 2D nanomaterials for biomedical applications.

Non-covalent functionalization relies on weak yet directional interactions such as electrostatic attraction, π–π stacking, hydrogen bonding, and host–guest inclusion. These interactions enable reversible and dynamic modification of 2D materials without disrupting their crystal frameworks.[173]

Electrostatic assembly is among the most widely employed methods, exemplified by the pairing of positively charged LDH nanosheets (LDH^+) with negatively charged biomolecules such as DNA^-, siRNA, or anionic drugs.[194–197] The strong Coulombic attraction facilitates high loading efficiency and controllable release through pH or ionic triggers.

Similarly, π–π stacking interactions are extensively utilized for loading aromatic drugs such as anthracyclines or porphyrins onto graphitic surfaces like graphene oxide (GO) or reduced GO. These interactions not only stabilize the drug within the 2D matrix but also enable light-induced electron transfer, supporting photothermal or photodynamic functionality.[198]

Hydrogen bonding provides another level of tunability, as seen in polydopamine (PDA) coatings, where catechol and amine groups interact with oxygenated functionalities on the 2D substrate to form a uniform, adhesive, and biocompatible shell. This coating serves as both a passivation layer and a reactive interface for secondary conjugation. [199]

In parallel, host–guest chemistry, using macrocyclic hosts such as cyclodextrins or cucurbiturils, allows encapsulation of small drug molecules or fluorescent dyes within a supramolecular cavity tethered to the 2D surface. Such reversible inclusion complexes enable stimuli-responsive loading and release, making them ideal for dynamic therapeutic systems.

While non-covalent strategies preserve the intrinsic conductivity, photothermal efficiency, and crystalline order of vdW materials, covalent functionalization introduces robust chemical bonds that resist desorption and degradation in physiological environments. These reactions often target defect sites, edge atoms, or functional groups on oxidized or functionalized 2D surfaces.

Among the most versatile approaches is click chemistry, particularly the azide–alkyne cycloaddition, which allows rapid and orthogonal coupling under mild conditions. This reaction has been exploited to tether polymers, peptides, and imaging agents to 2D materials with high yield and selectivity.

EDC/NHS-mediated amide coupling is another powerful route, commonly used to conjugate carboxyl or amine-containing biomolecules onto carboxylated graphene oxide, MoS_2, or LDH composites. This chemistry enables the stable attachment of antibodies, enzymes, or targeting ligands without compromising biological activity.[200]

Catechol/quinone grafting, inspired by the adhesive chemistry of polydopamine, introduces redox-active surface moieties capable of further crosslinking or coordinating metal ions. This strategy is particularly useful for constructing hierarchical architectures where interlayer adhesion and biological functionality must coexist.

Finally, thiol–ene and thiol–yne reactions provide efficient ways to functionalize unsaturated bonds or defect sites on 2D edges, enabling precise control over surface hydrophilicity, charge, and bioconjugation density. Together, these non-covalent and covalent functionalization strategies provide a comprehensive toolkit for transforming vdW nanohybrids from inert materials into biointeractive and programmable nanoplatforms. The choice of method is governed by the intended application: reversible and stimuli-responsive interactions are favored for dynamic therapeutic systems, while covalent linkages are indispensable for durable constructs intended for in vivo stability or long-term sensing. Ultimately, the rational combination of these approaches enables fine-tuned control over interfacial chemistry, paving the way toward multifunctional, adaptive vdW biointerfaces capable of integrating seamlessly within complex biological environments.

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Table 4 Overview of Non-Covalent and Covalent Functionalization Strategies for vdW Nanohybrids

Strategy Type	Mechanism	Typical Bonds/ Interactions	Applications in vdW Nanohybrids	Examples
Electrostatic Assembly *(Non-Covalent)*[174]	Coulombic attraction between oppositely charged surfaces[174]	$LDH^{+} \leftrightarrow DNA^{-}$,[175] $siRNA^{-}$,[176] drug anions	High loading efficiency,[74] pH/ion-triggered release	LDH–DNA,[175] LDH–siRNA,[176] DHT-Niclosamide (NIC)[74]
π–π Stacking *(Non-Covalent)*[174]	Face-to-face interaction between aromatic π systems[174]	Graphitic π surfaces ↔ aromatic drugs[177]	Drug loading, photothermal/PDT synergy, charge transfer[178]	GO–doxorubicin;[179] rGO–porphyrins[180]
Hydrogen Bonding *(Non-Covalent)*[181]	Directional H–bonding between donor/acceptor groups[181]	PDA catechols/ amines ↔ oxygenated 2D surfaces[182]	Uniform coatings, passivation, secondary conjugation[183]	PDA-coated BP,[184] PDA-coated LDH[184]
Host–Guest Inclusion *(Non-Covalent)*[185]	Supramolecular encapsulation inside macrocyclic cavities[185]	Cyclodextrin/ Cucurbituril ↔ small drug guests[186]	Stimuli-responsive loading/release, fluorescence modulation[187]	CD-functionalized GO;[188] CB[7] –dye complexes
Click Chemistry *(Covalent)*[189]	Azide–alkyne cycloaddition forming triazole linkages[189]	Strong C–N/C–C covalent bonds[189]	Stable polymer/peptide grafting; bioorthogonal conjugation[97]	GO–PEG–alkyne click;[190] Maleimide-functionalized adlayers[191]
EDC/NHS Amide Coupling *(Covalent)*[192]	Carboxyl–amine condensation forming amide bonds[192]	$COOH–NH_2$ bond formation[192]	Antibody/ligand immobilization, enzyme conjugation[192]	MXene –antibody[Xie, #
Catechol/Quinone Grafting *(Covalent)*[183]	Oxidative coupling or metal coordination via PDA-like motifs	C–C/C–O bonds + metal–catechol complexes	Adhesive layers, hierarchical assembly, redox-active shells	MXene functionalized with a tannic acid/cerium ammonium nitrate coordination complex and integrated into a waterborne polyurethane (WPU) polymer matrix to achieve pH-responsive passivation and self-healing properties[183]
Thiol–Ene / Thiol–Yne Reactions *(Covalent)*[193]	Radical addition of thiols to unsaturated bonds	C–S / C–C bonds	Edge functionalization, hydrophilicity tuning, crosslinking	Vinylene-Linked 2D Covalent Organic Frameworks (V-2D-COFs)[193]

Notes: This table summarizes the principal chemical mechanisms used to functionalize 2D van der Waals materials, highlighting their bonding interactions, advantages, and biomedical applications. Non-covalent strategies such as electrostatic assembly, π–π stacking, hydrogen bonding, and host–guest inclusion- enable reversible, lattice-preserving modifications ideal for dynamic therapeutic systems. In contrast, covalent approaches including click chemistry, EDC/ NHS coupling, catechol/quinone grafting, and thiol–ene reactions provide durable, chemically robust interfaces suited for long-term stability, targeting, or in vivo biointegration.

Ionic and Non-Ionic Strategies

The assembly and stabilization of vdW nanohybrids are equally governed by ionic and non-ionic interactions, which determine guest–host affinity, interlayer architecture, and the dynamic exchange of therapeutic payloads. Unlike covalent or purely supramolecular approaches, ionic and non-ionic strategies exploit the intrinsic charge characteristics of many 2D materials, particularly clays, LDHs, and other charged lamellar oxides, to achieve highly efficient and controllable loading of bioactive molecules. These interactions are central to designing nanohybrids with programmed release profiles, tunable biocompatibility, and selective targeting capability.[201]

Ionic strategies leverage the presence of interlayer cations (eg, Mg^{2+}, Zn^{2+}, Ca^{2+}) or positively charged laminates to anchor oppositely charged therapeutic molecules. Classic examples include:

- Cationic LDHs (eg, Mg–Al, Zn–Al, Ca–Al LDHs) intercalating anionic drugs, siRNA, Methotrexate, or anti-inflammatory molecules through anion-exchange or electrostatic uptake.
- Layered silicates such as MMT or hectorite, which possess negatively charged sheets, binding cationic peptides, proteins, or metal complexes within their hydrated galleries.
- Calcium-based layered materials (eg, Ca–Al layered oxides) form stable ionic host–guest complexes with phosphate-containing biomolecules or carboxylate-functional therapeutics.

These ionic interactions create robust yet stimuli-responsive assemblies in which pH, ionic strength, or competitive anions can modulate drug retention and release; an ideal feature for inflammatory, tumor, or wound microenvironments.

Non-ionic strategies rely on vdW attractions and other weak, non-electrostatic forces to load or anchor neutral guest molecules onto 2D materials. Unlike ionic interactions, these mechanisms do not depend on positive or negative charge. Instead, they arise from natural surface forces present on layered hosts such as LDHs, MMT, laponite, and calcium-based clays. Because these interactions are mild and reversible, the 2D structure remains intact and the guest molecules retain their biological activity.

Common examples include hydrophobic drugs fitting into partially dehydrated LDH or clay galleries, where the close contact between layers generates vdW attraction and dipole–induced dipole interactions that stabilize the drug inside the host. Neutral small molecules such as vitamins, polyphenols, antioxidants, or growth factors binding to clay or LDH surfaces through vdW forces and weak hydrogen bonding, enabling gentle loading without chemical modification.

Neutral polymers like PEG, PVP, or HPMC forming soft, non-ionic coatings on 2D surfaces. These steric layers improve colloidal stability, prevent aggregation, and enhance biocompatibility while leaving the underlying vdW interfaces accessible for biological interactions.

Taken together, ionic and non-ionic strategies expand the chemical palette for building vdW nanohybrids, offering pathways for both strong, charge-governed immobilization and gentle, reversible incorporation of therapeutics. Their orthogonality allows fine-tuning of loading capacity, release kinetics, and biological response key parameters for advancing vdW platforms in drug delivery, immunomodulation, tissue repair, and precision nanomedicine.

Biological Coronas and Stealth

In physiological environments, the biological corona can itself be understood as a soft, adaptive 2D vdW layer. Upon exposure to biological fluids, proteins, lipids, and metabolites spontaneously spread over the nanoparticle surface, forming an ultrathin film held together by vdW, hydrophobic, and weak polar interactions. This corona behaves like a quasi-2D nanosheet, reshaping the interface without altering the underlying material. However, this spontaneous layer acts as a "gatekeeper"[202] that redefines the particle's biological identity and frequently masks synthetic targeting ligands. To circumvent this, dual-targeting biomimetic strategies[203] utilize pre-engineered membranes to outcompete this random protein adsorption, preserving ligand accessibility for precision therapy.

Once introduced into physiological fluids, vdW nanohybrids are rapidly enveloped by this biological corona, a dynamic layer of biomolecules that adsorbs within seconds and ultimately determines the particle's "biological identity". The corona governs cellular perception, immune clearance, tissue targeting, and biodistribution. Although it

Table 5 Biological Corona Formation and Stealth Engineering in vdW Nanohybrids

Process/Strategy	Mechanism	Key Effects on vdW Nanohybrids	Advantages	Limitations
Biological Corona Formation[205]	Rapid adsorption of proteins, lipids, metabolites upon exposure to physiological fluids[205]	Defines the nanoparticle's "biological identity"; masks targeting ligands; alters charge and colloidal behavior[97]	Enables natural interactions; may assist in cell recognition depending on corona composition[97]	Uncontrolled opsonization, immune clearance, altered biodistribution[97]
PEGylation (Polyethylene Glycol)[206]	Hydrated polymer brush forms steric barrier[206]	Reduces protein binding; prolongs circulation; decreases macrophage uptake[206]	Excellent antifouling; widely validated clinically[206]	Excess PEG reduces cellular uptake, endosomal escape, and may induce "accelerated blood clearance" with repeat dosing[206]
Zwitterionic Polymer Coating[97]	Hydration shell formed via charge-balanced groups (eg, sulfobetaine)	Minimizes nonspecific adsorption; maintains stability at physiological ionic strength	Strong long-term antifouling; non-immunogenic	Fewer clinical precedents than PEG; synthesis sometimes complex
Biomimetic Membrane Cloaking[207]	Coating with natural RBC, platelet, or cancer-cell membranes	Presents native surface antigens; provides immune self-recognition; reduces phagocytosis	Superior immune evasion; enhanced circulation and barrier navigation	Source-dependent variability; stability and scale-up challenges[207]
Size Optimization (30–80 nm lateral)[208]	Engineering nanosheets or stacks to optimal dimensions	Enhances ECM penetration; avoids renal clearance; improves EPR-like effects	Balanced biodistribution and retention	Too small → rapid filtration; too large → poor tissue penetration[208]
Surface Charge Modulation (Near-neutral ζ-potential)[209]	Control of terminal functional groups, coatings, or corona composition	Reduces nonspecific interactions with proteins/membranes; enhances deep tissue diffusion	Improved circulation + reduced clearance	Over-neutralization may reduce targeting efficiency
Ligand Conjugation (Active Targeting)[210]	RGD, folic acid, antibodies, aptamers bind overexpressed receptors	Enables receptor-mediated uptake; enhances localization in diseased tissues	High specificity and precision	Ligand masking by corona if not appropriately engineered
Dual Strategy: Stealth + Targeting[211]	Sequential coating (stealth) followed by ligand presentation	Maximizes selectivity, circulation, and accumulation	Best-in-class biodistribution and therapeutic efficacy	Requires precise control of ligand exposure post-coating

Notes: Upon exposure to physiological fluids, vdW nanohybrids rapidly acquire a biological corona that determines their molecular identity and interaction with immune and cellular systems. Stealth strategies including PEGylation, zwitterionic coatings, and biomimetic membrane cloaking are employed to limit opsonization, prolong circulation, and modulate biodistribution. Additional engineering of particle size, surface charge, and receptor-specific ligands enables synergistic immune evasion and targeted delivery. Together, these design principles transform vdW nanohybrids into adaptive biological entities capable of selective tissue penetration, prolonged bioavailability, and optimized therapeutic precision.

may mask engineered ligands or alter surface charge, the corona also presents an opportunity for controlled interface engineering, transforming a natural phenomenon into a programmable design feature.

To contextualize how vdW nanohybrids interact with physiological environments, Table 5 summarizes the major mechanisms governing biological corona formation and stealth engineering, along with their implications for biodistribution and immune recognition. To mitigate uncontrolled opsonization and immune recognition, vdW nanohybrids are frequently pre-coated with stealth materials such as PEG, zwitterionic polymers, or natural biomembranes. PEGylation creates a hydrated steric barrier that minimizes nonspecific protein adsorption and prolongs systemic circulation, yet excessive PEG density can hinder cellular uptake or endosomal escape.[204] In addition sometimes, PEGylation can present certain limitations, including accelerated blood clearance upon repeated administration and potential immunogenic responses in some cases.

Zwitterionic coatings,[212] composed of sulfobetaines or carboxybetaines, offer an alternative antifouling mechanism through charge neutrality and strong hydration shells, providing long-term colloidal stability under physiological ionic strength. More recently, biomimetic membrane cloaking using red blood cell, platelet, or cancer-cell membranes has emerged as a powerful strategy to confer immune self-recognition. These membrane coatings preserve surface antigens

and adhesion molecules from their source cells, allowing vdW nanohybrids to evade phagocytic clearance and navigate biological barriers with native-like behavior.

Beyond immune evasion, stealth engineering influences biodistribution and targeting efficiency. Controlled modulation of size, surface potential, and ligand presentation ensures that vdW nanohybrids can accumulate preferentially in diseased tissues through both passive and active mechanisms.[213] Optimal dimensions typically lie in the 30–80 nm lateral range, small enough to penetrate the dense ECM yet large enough to avoid rapid renal filtration. Maintaining a near-neutral zeta potential minimizes nonspecific electrostatic interactions with serum proteins and cellular membranes, further promoting deep tissue diffusion.[214]

To enhance specificity, targeting ligands such as RGD peptides, folic acid, antibodies, and nucleic acid aptamers can be conjugated to the outermost layer of vdW nanohybrids. These ligands engage overexpressed receptors on tumor or inflamed cells, facilitating receptor-mediated endocytosis and localized therapeutic action. When combined with stealth coatings, the dual strategy of immune evasion and active targeting ensures high selectivity and prolonged bioavailability —a prerequisite for effective precision nanomedicine.

Ultimately, mastering biological corona formation and stealth engineering transforms vdW nanohybrids from passive colloids into adaptive biological entities. By understanding and controlling the interplay between synthetic surfaces and biological fluids, researchers can dictate the circulation lifetime, immune interactions, and organ tropism of these materials. Such insight is pivotal for translating vdW nanohybrids into clinically viable, safe, and intelligent nanoplatforms capable of harmonizing with the body's own molecular logic.

Structure–Property Relationships Relevant to Biology

The biomedical behavior of vdW nanohybrids is dictated by a finely tuned interplay between their structural attributes and physicochemical properties. Unlike conventional isotropic nanoparticles, 2D architectures exhibit unique anisotropy, large aspect ratios, and layer-dependent quantum and catalytic effects that directly influence their optical performance, charge transport, mechanical flexibility, and biodegradation. Understanding these structure–property–function relationships is therefore essential to designing vdW systems that are both therapeutically effective and biologically compatible.

Optical properties form one of the most powerful dimensions of vdW nanohybrids. Materials such as MXenes, TMDs, black phosphorus (BP), and rGO exhibit strong absorption in the near-infrared (NIR) regions (NIR-I, 700–950 nm; NIR-II, 1000–1350 nm), enabling deep-tissue photothermal therapy (PTT) and high-contrast imaging.[215] The broad and tunable plasmonic response of MXenes and the excitonic transitions in TMDs allow efficient light-to-heat conversion even at low power densities, while BP's thickness-dependent bandgap ensures wavelength-selective photonic control. To further extend functionality, upconversion nanoparticles or persistent luminescent coatings are often integrated into vdW frameworks, converting low-energy NIR light into higher-energy emissions that can activate photosensitizers for photodynamic therapy (PDT) at reduced fluence, minimizing phototoxicity to healthy tissues.[216]

Beyond optical activity, electronic and ionic conductivity play crucial roles in mediating biological communication and electrical interfacing. Conductive 2D materials such as MXenes and graphene can serve as bioelectronic transducers, bridging the gap between living tissue and electronic devices. Their high carrier mobility, large interfacial area, and impedance matching enable stable integration with excitable tissues like nerve and cardiac muscle. Such properties facilitate applications in neural recording, cardiac pacing, and electro-triggered drug release, where electric fields or currents are used to modulate the transport or conformation of therapeutic molecules embedded within vdW layers.

In parallel, the intrinsic catalytic and enzyme-mimetic activities of certain 2D materials have unlocked new biochemical functionalities. TMDs, MXenes, and 2D metal–organic frameworks (2D-MOFs) display peroxidase-, catalase-, and oxidase-like activities, allowing them to generate or scavenge reactive oxygen species (ROS) in situ. These properties can be harnessed for chemodynamic tumor therapy, antibacterial disinfection, or oxidative stress modulation in inflamed tissues. The catalytic performance is highly structure-dependent—controlled by metal centers, defect density, and surface terminations and can be dynamically tuned through vdW stacking or interfacial charge transfer, providing a versatile platform for redox-based biomedical regulation.

The mechanical flexibility of few-layer 2D materials further enhances their biological compatibility. Their high aspect ratio and deformability enable close conformal contact with soft tissues, reducing local mechanical irritation and

inflammatory responses compared to rigid or spherical nanoparticles. Cellular internalization is also strongly influenced by lateral size and aspect ratio: smaller nanosheets typically enter cells via clathrin-mediated endocytosis, while larger or flexible flakes favor macropinocytosis or membrane wrapping. Thus, geometry acts as a critical determinant of biodistribution, intracellular trafficking, and clearance.

Degradability and metabolic transformation are equally pivotal for long-term biosafety. Materials such as BP degrade into innocuous phosphate ions under physiological conditions,[217] while LDHs dissolve into biocompatible cations such as Mg^{2+}, Al^{3+}, or Zn^{2+}.[218] Graphene-based materials exhibit slower degradation kinetics, but their persistence can be mitigated through oxidative pathways mediated by enzymes like myeloperoxidase or by downsizing to ultrasmall fragments. In contrast, MXenes undergo gradual oxidation in aqueous or biological environments, generating TiO_2-like phases that can be protective or functional depending on the coating and surface chemistry. Strategic surface passivation or polymer encapsulation is often employed to modulate degradation kinetics and maintain performance during therapy.

Finally, safety and immunocompatibility represent the ultimate benchmark for biomedical translation. The sharp edges and high surface reactivity of some 2D materials can induce hemolysis or membrane perturbation, but these risks are significantly reduced through hydrophilic coatings, charge neutralization, or control of edge chemistry. Moreover, ensuring endotoxin-free synthesis and rigorous pyrogen testing is essential before any in vivo application to prevent immune activation or inflammatory cascades. Comprehensive assessment of hemocompatibility, complement activation, and long-term biodistribution remains a prerequisite for clinical validation.

In sum, the biological fate and functionality of vdW nanohybrids arise from an intricate coupling between structure and property. By rationally tuning optical, electronic, catalytic, mechanical, and degradative characteristics, researchers can tailor these materials to harmonize with complex physiological systems—transforming them from simple layered constructs into bioresponsive, multifunctional architectures capable of precise therapeutic action and real-time biological integration.

Recent Biomedical Application Landscape

The expanding biomedical scope of vdW nanohybrids reflects their unprecedented ability to integrate multiple therapeutic and diagnostic modalities within a single, atomically precise platform. Their modular stacking and tunable interlayer chemistry enable synergistic interactions—photothermal, catalytic, electronic, and immunological—that can be orchestrated for disease-specific interventions. Across oncology, infectious disease, tissue engineering, and biosensing, vdW systems bridge the divide between materials science and functional medicine, providing responsive, multifunctional solutions to longstanding clinical challenges.

Cancer Theranostics

Cancer therapy represents one of the most extensively explored application domains for van der Waals (vdW) nanohybrids, where the integration of photothermal conversion, drug delivery, and immunomodulation can produce synergistic therapeutic outcomes. In PTT, layered materials such as MXenes, rGO, and BP efficiently convert NIR-I/II irradiation into localized hyperthermia, enabling selective tumor ablation. When laminated with layered double hydroxides (LDH), these photothermal nanosheets can simultaneously function as drug reservoirs, allowing co-delivery of chemotherapeutic agents such as doxorubicin or gene cargos, including siRNA. Such vdW-integrated systems enable coordinated thermal and molecular therapy with precise spatiotemporal control.

In photodynamic therapy (PDT), transition-metal dichalcogenides (TMDs) and 2D metal–organic frameworks (2D-MOFs) can act either as intrinsic photosensitizers or as carriers for porphyrins and phthalocyanines. vdW stacking within these architectures reduces chromophore self-quenching while catalytic interlayers improve oxygen availability in hypoxic tumors, thereby enhancing reactive oxygen species (ROS) production and tumor cytotoxicity.

Representative biomedical implementations of vdW Ti_3C_2 MXene nanosheets further illustrate the translational potential of these materials. In one approach, Ti_3C_2 nanosheets are incorporated into a thermosensitive Pluronic F127 hydrogel to create an injectable photothermal platform for localized treatment of uterine sarcoma. The mildly oxidized MXene nanosheets preserve their intrinsic layered vdW structure while exhibiting enhanced photothermal

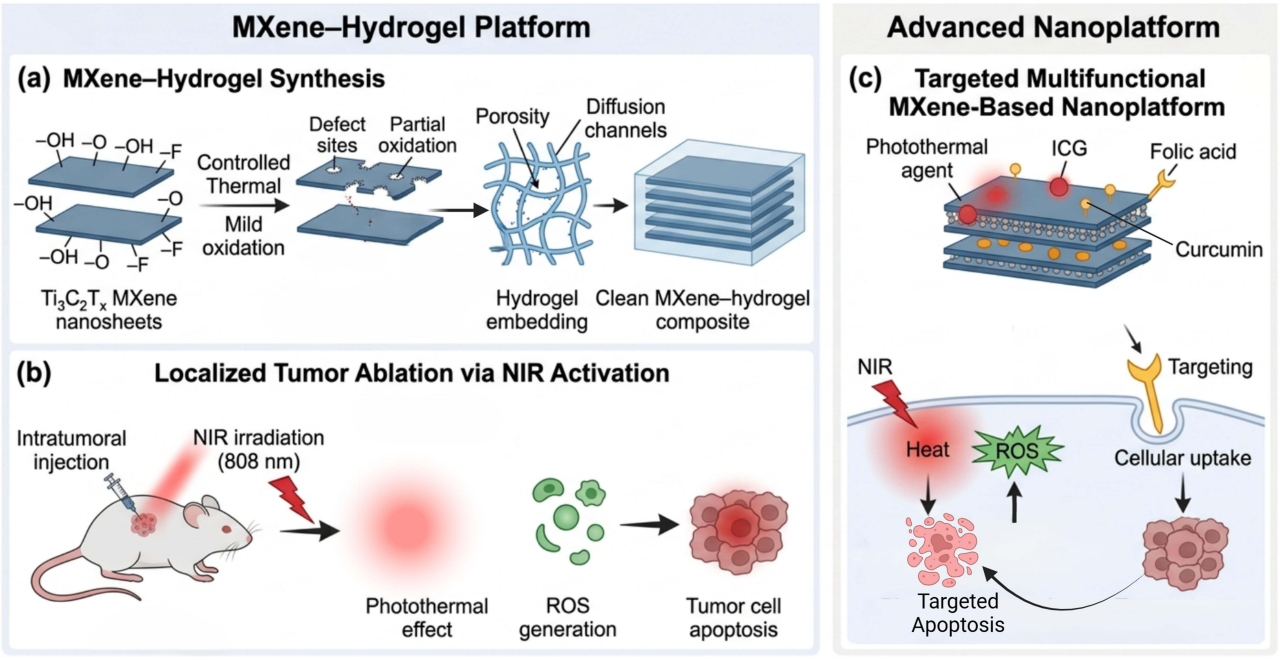

Figure 2 MXene-based van der Waals (vdW) nanoplatforms for photothermal and photodynamic cancer therapy. (**a**) Preparation of MXene–hydrogel composite platform. MXene nanosheets undergo controlled thermal oxidation treatment to generate mildly oxidized MXene nanosheets, which are subsequently integrated within a hydrogel matrix to form a MXene–hydrogel composite. This hybrid structure enhances photothermal conversion efficiency and reactive oxygen species (ROS) generation under near-infrared (NIR) irradiation. (**b**) Intratumoral delivery and tumor ablation. The MXene–hydrogel composite is administered via intratumoral injection, followed by NIR laser irradiation. The photothermal effect and ROS production induce localized tumor destruction and apoptosis of tumor cells. (**c**) Surface-functionalized vdW MXene nanoplatform for synergistic therapy. Ti_3C_2 MXene nanosheets are produced through chemical etching and sonochemical delamination, followed by surface functionalization with targeting ligands (eg, folic acid) and therapeutic/photonic agents such as indocyanine green (ICG) and curcumin (Cur). Under NIR irradiation, the platform enables combined photothermal and photodynamic therapy through heat generation and ROS production, resulting in targeted tumor cell apoptosis. Data from references [219] and [80].

conversion and ROS generation. The surrounding hydrogel matrix provides a biocompatible environment that stabilizes nanosheet dispersion and enables sustained therapeutic activity, resulting in efficient tumor ablation with minimal off-target toxicity (Figure 2a-b). [219]

In another strategy, Ti_3C_2 MXene nanosheets serve as vdW substrates for non-covalent functionalization with folic acid, indocyanine green (ICG), and curcumin. Surface decoration through π–π interactions, hydrogen bonding, electrostatic attraction, and weak vdW forces produces a multifunctional biointerface capable of simultaneous photothermal and photodynamic activity under NIR irradiation. The layered MXene architecture preserves high surface area and optical responsiveness while enabling targeted drug delivery and controlled therapeutic release, demonstrating the versatility of vdW nanosheet platforms for precision cancer phototherapy (Figure 2c). [80]

Beyond photothermal and photodynamic modalities, vdW nanohybrids are increasingly engineered to modulate immune responses within diseased tissues. Layered double hydroxide (LDH) systems, for example, can reshape inflammatory microenvironments by buffering local pH, scavenging pathogenic mediators, and regulating nucleocytoplasmic signaling pathways. Surface-functionalized variants such as folic-acid-modified LDH (FA-LDH) retain their intrinsic vdW layered architecture while enabling selective targeting of activated macrophages. Through regulation of Smad5 transport and suppression of NF-κB signaling, FA-LDH promotes macrophage repolarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 state, demonstrating how vdW nanomaterials can actively reprogram immune microenvironments in diseases such as rheumatoid arthritis (Figure 3). [220]

An emerging dimension involves ECM normalization, where LDH layers buffer acidity, PDA or ceria components scavenge ROS, and loaded inhibitors block YAP/TAZ or STAT3 signaling. By softening and reprogramming the tumor microenvironment, such hybrids enhance drug penetration and counteract the phenomenon of pseudo-resistance that often limits cancer therapy.

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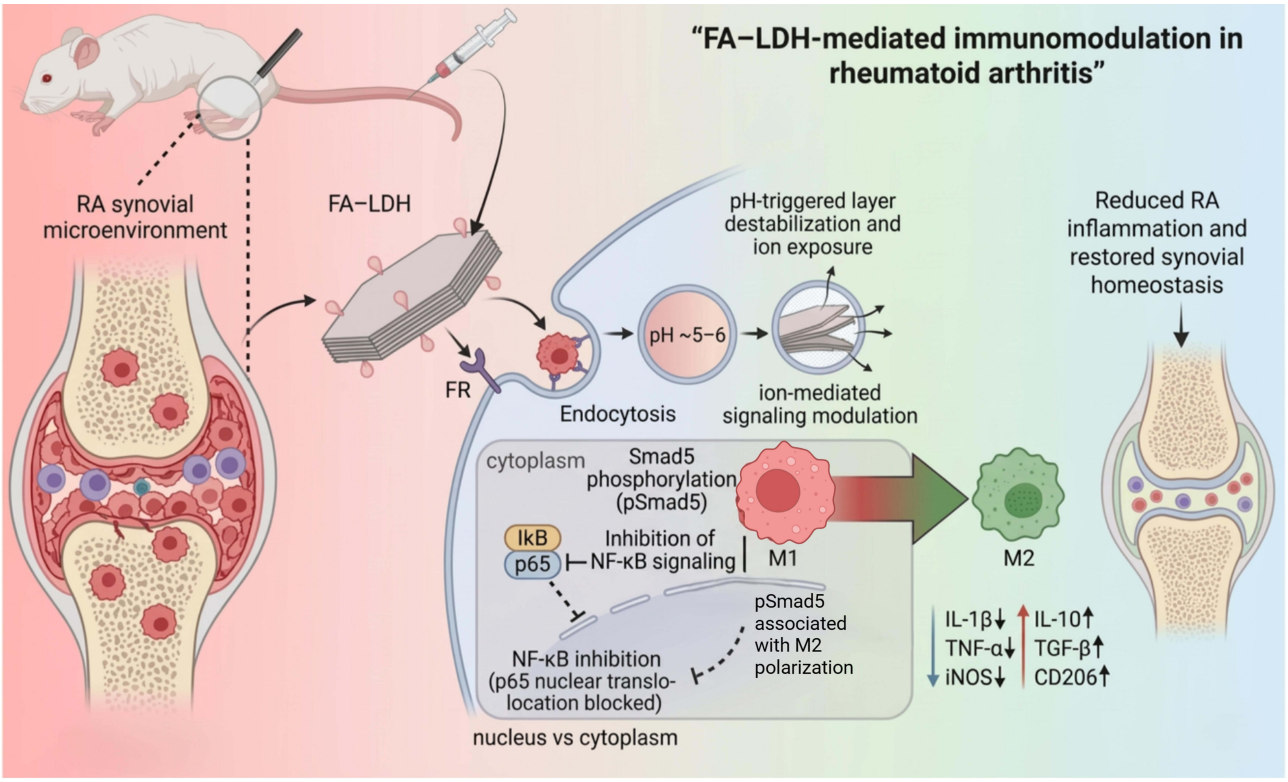

Figure 3 FA-LDH nanoplatform for targeted immunomodulation and macrophage repolarization in rheumatoid arthritis (RA). Conceptual illustration of the therapeutic mechanism of folic acid–functionalized layered double hydroxide nanoparticles (FA-LDH) in RA treatment. Following intra-articular or systemic administration, FA-LDH nanoparticles preferentially accumulate in inflamed RA joints characterized by synovial inflammation, immune cell infiltration, and bone erosion. FA-LDH nanoparticles selectively target activated macrophages through folate receptor–mediated recognition and are internalized via receptor-mediated endocytosis. Under acidic intracellular conditions, FA-LDH nanoparticles undergo pH-responsive release, modulating intracellular signaling pathways. Specifically, FA-LDH regulates Smad signaling while suppressing NF-κB activation through inhibition of the p65/IκB pathway. This signaling modulation reduces the expression of pro-inflammatory mediators (iNOS, IL-1β, TNF-α) and promotes anti-inflammatory cytokines (TGF-β, IL-10). As a result, pro-inflammatory M1 macrophages are repolarized toward the anti-inflammatory M2 phenotype (CD206^{+}), contributing to attenuation of synovial inflammation and restoration of immune homeostasis in RA joints. Adapted from Ref.[220]

Anti-Infectives and Wound Care

Among emerging anti-infective platforms, vdW-based nanozyme hybrids such as MXene–LDH constructs offer a powerful strategy for overcoming microbial resistance and supporting wound healing. The V_2CT_x-MXene@NiCuFe-LDH (MNCF) nanozyme exemplifies this approach: as a 2D–2D vdW heterostructure, it integrates the strong electron-transfer capacity of MXene with the redox-active catalytic centers of LDH to achieve robust peroxidase-like activity. This synergistic interface drives efficient ROS generation, GSH depletion, and broad-spectrum bactericidal action against *E. coli*, *S. aureus*, and MRSA while maintaining excellent biocompatibility. Beyond direct antimicrobial effects, the sustained catalytic ROS production and high surface reactivity of such vdW nanozymes can disrupt biofilms, prevent recolonization, and modulate the wound microenvironment to promote cleaner, infection-resistant tissue beds. These attributes position MXene–LDH heterostructures as promising vdW nanozymes for next-generation antimicrobial dressings, wound-healing hydrogels, and anti-biofilm coatings.[221]

Neurointerfaces and Bioelectronics

Owing to their exceptional conductivity, mechanical compliance, and biocompatibility, vdW nanohybrids are emerging as ideal materials for neural interfacing. MXene/graphene laminates provide low-impedance, high-fidelity electrodes for EEG, ECoG, and deep-brain stimulation, maintaining stable contact with soft neural tissue. Hybridization with hydrogels or surface gels mitigates inflammatory encapsulation and enhances long-term recording stability. In addition to passive sensing, vdW electrodes enable active neuromodulation and drug delivery: electrophoretic or electrochemical gradients across conductive layers permit spatially precise release of neurotransmitters or anti-inflammatory agents, offering

controllable neuromodulatory interventions. However, long-term in vivo evaluations remain limited. Critical factors such as chronic recording stability beyond several months, glial scar formation, and neuroinflammatory responses must be systematically assessed before claims of stable long-term neural interfacing can be fully validated. Future studies focusing on chronic implantation models and histological evaluation of neural tissue responses will be essential to establish the clinical viability of vdW-based neural interfaces.

Lately MXenes nanosheets were shown to markedly enhance the direct lineage reprogramming of induced dopaminergic (iDA) neurons both in vitro and in vivo. The vdW-layered MXene structure provides a functionalizable, conductive surface that efficiently transduces electromagnetic field (EMF) stimuli into intracellular biochemical responses. This coupling selectively promotes histone acetylation during neuronal reprogramming, thereby accelerating dopaminergic lineage specification and improving functional outcomes in a Parkinson's disease mouse model. Notably, MXene-mediated EMF stimulation also enabled the reprogramming of human skin fibroblasts into iDA neurons with enhanced efficiency and reliability. Together, these findings highlight vdW MXene nanosheets as a next-generation bioelectronic platform for epigenetic modulation, neural reprogramming, and regenerative medicine.[222]

Cardiovascular and Musculoskeletal Regeneration

In cardiac repair, conductive vdW patches composed of MXene, graphene, or PDA-LDH laminates synchronize cardiomyocyte contraction and support electrical signal propagation across infarcted regions. These platforms also serve as reservoirs for pro-regenerative molecules or exosomes, combining electrical pacing with biochemical stimulation. In orthopedics, bone-integrated vdW hybrids incorporating LDHs or bioactive oxides release osteogenic ions (Mg^{2+}, Zn^{2+}, Ca^{2+}) that promote mineralization, while mild photothermal pulses induce vascularization and accelerate bone–implant integration.

The recent study on MgSrCeAl-LDH nanosheets represent a potent class of vdW bioactive therapeutics for myocardial ischemia/reperfusion (I/R) injury. As 2D vdW LDH layers, they combine intrinsic ROS-scavenging activity with ischemia-responsive ion release to simultaneously address oxidative damage and impaired revascularization. The nanosheets efficiently neutralize ·OH and $\cdot O_2^-$ radicals exceeding the activity of CeO_2—and release angiogenic Sr^{2+} under the acidic conditions of ischemic myocardium, promoting robust neovascularization. In vivo, MgSrCeAl-LDH treatment reduced myocardial ROS levels to 66.2% of baseline and increased vascular density by approximately 3.6-fold, ultimately decreasing infarct size by 60.9%. Mechanistically, these vdW nanosheets protect the myocardium by activating the PI3K/Akt pathway while suppressing TGF-β signaling, thereby mitigating fibrosis and improving cardiac function. This work highlights the emerging potential of vdW LDH nanosheets as multifunctional cardiovascular therapeutics capable of coordinated ROS regulation, angiogenesis, and tissue remodeling (Figure 4).[223]

Biosensing and Diagnostics

The atomically thin, high-surface-area nature of vdW assemblies makes them powerful transduction elements for biosensing. Electrochemical sensors leveraging MXenes, graphene, or 2D-MOFs exhibit high catalytic activity and low charge-transfer resistance, enabling real-time detection of biomarkers such as glucose, lactate, cytokines, or circulating tumor DNA. Optical biosensors utilize the luminescent or photoacoustic properties of BP, 2D-COFs, and porphyrin-based MOFs for multiplexed, deep-tissue imaging. Extending beyond laboratory diagnostics, wearable vdW devices integrate sensing and actuation—MXene/graphene patches capable of monitoring strain, sweat metabolites, and temperature while autonomously triggering drug release or photothermal therapy in a feedback loop.

For example, lately NiMn-LDH–eM was developed as a prototypical vdW 2D–2D nanozyme heterostructure designed for neurochemical diagnostics. In this architecture, NiMn-LDH nanosheets are grown in situ onto exfoliated MXene substrates, forming an intimate vdW-coupled interface that greatly enhances oxidase-like catalytic activity (3.6 U mg^{-1}). This catalytic synergy enables highly sensitive dopamine detection through a tri-modal readout integrating UV–vis absorbance, Si-QD-assisted ratiometric fluorescence, and electrochemical signals. Dopamine competitively consumes catalytic intermediates, resulting in decreased DAP formation, a reduced F565/F453 fluorescence ratio, diminished DAP absorption at 450 nm, and amplified electrochemical current. Together, this vdW heterointerface nanozyme offers a robust and multifunctional platform for early neurodegenerative disease diagnostics.[224]

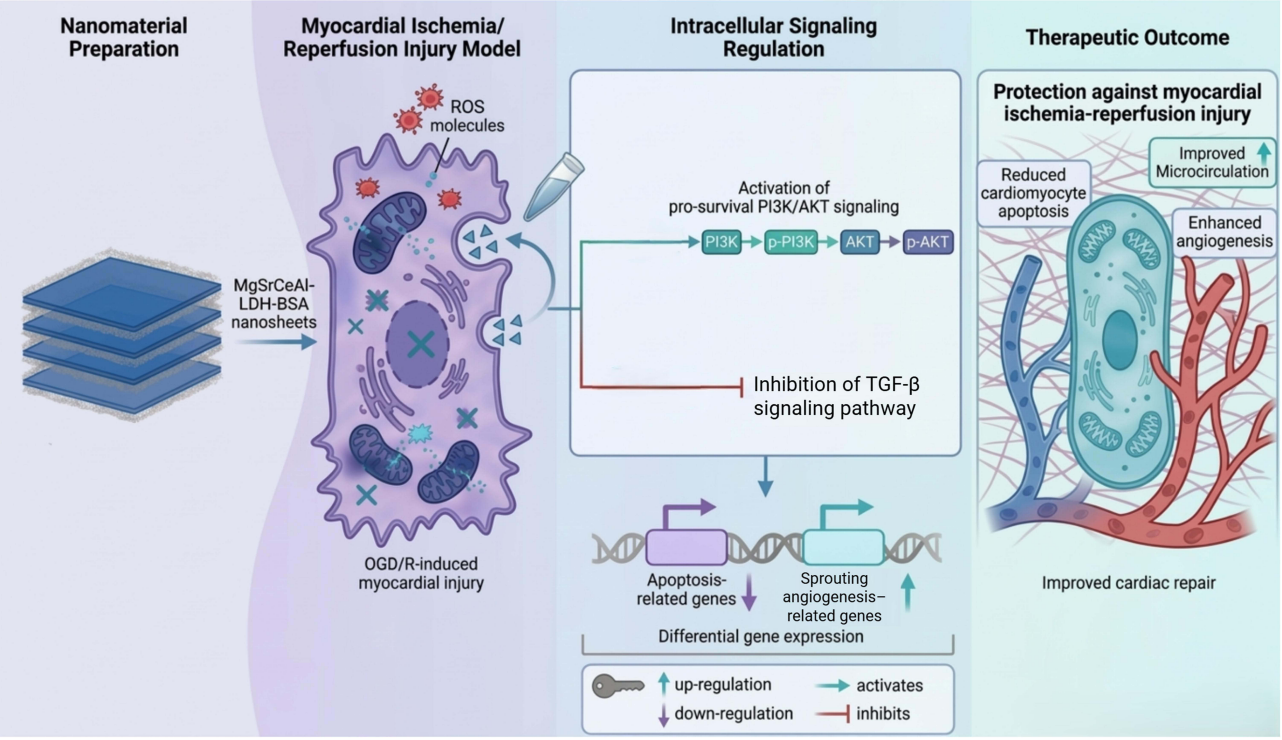

Figure 4 Conceptual illustration of MgSrCeAl-LDH-BSA nanosheets for protection against myocardial ischemia–reperfusion (I/R) injury. Ultrathin MgSrCeAl-LDH-BSA layered double hydroxide (LDH) nanosheets are delivered to cardiomyocytes under oxygen–glucose deprivation/reperfusion (OGD/R) conditions, a cellular model of myocardial I/R injury characterized by elevated ROS and cellular stress. The LDH nanosheets modulate intracellular signaling pathways, including activation of the PI3K/AKT pathway and modulation of TGF-β/Smad signaling, potentially attenuating ROS-associated stress. These effects regulate downstream gene expression, including suppression of apoptosis-related genes and upregulation of angiogenesis-related genes. Collectively, these responses reduce cardiomyocyte apoptosis and are associated with cardioprotection against myocardial ischemia–reperfusion injury. Adapted from Ref.[223]

Similarly, MXene-based CRISPR biosensors represent a powerful class of surface-engineered vdW platforms for infectious disease diagnostics, exemplified by the MXene–Au nanosheet dual-mode endotoxin sensor. In this construct, Au-modified MXene nanosheets serve as a vdW 2D scaffold capable of simultaneously quenching fluorophores and amplifying SERS signals, enabling a single-reporter Cy5–ssDNA probe to function in a ratiometric FL/SERS configuration. The CRISPR/Cas12a module selectively cleaves the Cy5 probe only in the absence of endotoxin, producing an "FL on/SERS off" signature, whereas intact Cy5 on the MXene–Au surface generates an "FL off/SERS on" state in the presence of endotoxin. This vdW-assisted dual-mode design enhances sensitivity, lowers the LOD to 15.9 pg/mL, and provides built-in cross-validation for improved reliability in complex matrices such as milk and environmental water samples. Such MXene-based vdW biosensors highlight the growing utility of 2D material interfaces for rapid, sensitive, and interference-resistant pathogen and endotoxin detection.[225]

Another study on Ti_3C_2 MXene acts as a conductive vdW nanosheet scaffold that enhances electron transfer and supports high-density loading of PEI–Ru luminophores and AuNPs. Target binding initiates an ISDA reaction that generates abundant dsDNA activators, triggering CRISPR/Cas12a trans-cleavage of ferrocene-labeled DNA probes on the electrode surface. Cleavage removes the quenching Fc group and restores strong Ru-based ECL emission, enabling highly sensitive, signal-on detection. The biosensor achieves an impressive detection limit of 1.67 aM, broad linear range, and excellent specificity for miR-31, with successful validation in human serum samples. This vdW-enhanced ECL–CRISPR platform demonstrates the powerful synergy between 2D MXene interfaces and nucleic-acid-driven amplification for early cancer biomarker detection and point-of-care diagnostic applications.[226]

The folate receptor (FR), overexpressed in many solid tumors, is an established target for cancer imaging and precision diagnostics. In this study, a dual-function 2D vdW nanoplatform is engineered using LDH nanoplates atomically thin inorganic sheets whose layers are held together by weak vdW forces, enabling high surface area, facile

functionalization, and efficient molecular interfacing. This vdW architecture allows the simultaneous integration of a targeting ligand and a multimodal imaging payload.

To achieve FR-specific cancer detection, LDH nanoplates were functionalized with FA as the targeting moiety and indocyanine green (ICG) as the near-infrared fluorescence agent, followed by radiolabeling with[62] Cu to create a PET/NIRF dual-imaging probe (^{64}Cu-LDH–ICG/FA). A non-targeted control (^{64}Cu-LDH–ICG) was prepared in parallel. The uptake of these vdW nanohybrids was evaluated across cancer cell lines with distinct FR expression levels (A549, H460, KB, HeLa).

A strong correlation emerged: cells with higher FR expression demonstrated markedly enhanced uptake of ^{64}Cu-LDH–ICG/FA, as reflected by both radioactivity and fluorescence intensity. In vivo PET and NIRF imaging further confirmed preferential accumulation in HeLa tumors (high FR) compared with A549 and KB models (lower FR).

Overall, this FR-targeted 2D vdW LDH nanoplate demonstrates high diagnostic sensitivity, outstanding tumor selectivity, and robust multimodal imaging performance, highlighting its strong potential for clinical translation in cancer theranostics.[62] (Figure 5).

Antiviral Therapy

Viral infections remain a global biomedical challenge, characterized by rapid mutation, immune evasion, and the emergence of drug-resistant or persistent viral reservoirs. The structural versatility of vdW nanohybrids—built from layered MXenes, LDHs, graphene derivatives, and 2D MOFs positions them as powerful antiviral platforms capable of combining direct virucidal action with immune modulation, mucosal protection, and targeted intracellular delivery. Unlike conventional antivirals that target single pathways, vdW interfaces enable multi-mechanistic antiviral logic, integrating photothermal, catalytic, electrostatic, and gene-silencing capabilities within a single material framework.

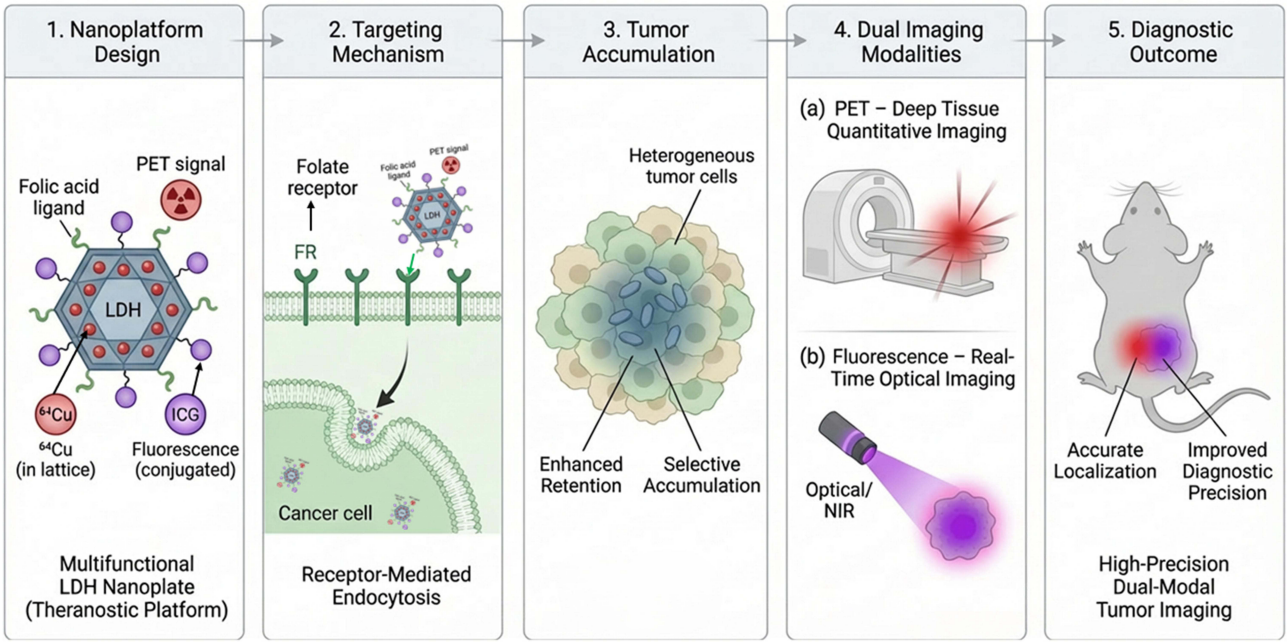

Figure 5 Design, targeting, and dual-modal imaging of folate-functionalized LDH nanoplatform. Schematic illustration of a multifunctional layered double hydroxide (LDH)-based nanoplatform engineered for targeted tumor imaging. (1) Nanoplatform design: LDH nanoplates are functionalized with folic acid ligands for receptor targeting, radiolabeled with ^{64}Cu within the lattice for positron emission tomography (PET), and conjugated with near-infrared (NIR) fluorescent probes (eg, ICG) for optical imaging. (2) Targeting mechanism: The nanoplatform selectively binds to folate receptors (FR) overexpressed on cancer cells and undergoes receptor-mediated endocytosis. (3) Tumor accumulation: Following systemic administration, nanoparticles exhibit preferential accumulation and retention within heterogeneous tumor tissues, driven by receptor-mediated uptake and microenvironmental interactions. (4) Dual imaging modalities: The integrated platform enables (a) PET imaging for deep-tissue, quantitative whole-body detection, and (b) NIR fluorescence imaging for real-time, high-resolution optical visualization. (5) Diagnostic outcome: The combined imaging approach improves tumor localization and enhances diagnostic precision through complementary sensitivity and spatial resolution. Adapted from Ref.[62]

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Photothermal Antiviral Activity

MXenes, graphene oxide (GO), and black phosphorus (BP) nanosheets exhibit strong NIR absorption and rapid heat conversion, enabling viral inactivation through localized hyperthermia. This mechanism is agnostic to viral genotype, making it particularly valuable against rapidly evolving pathogens such as SARS-CoV-2, influenza, or emerging zoonotic viruses. vdW assembly allows photothermal layers to be paired with LDH- or MOF-based catalytic sheets, creating antiviral surfaces for masks, filters, wound dressings, and surface coatings that achieve rapid viral inactivation under low-intensity light exposure.

Electrostatic and Interfacial Viral Trapping

Many viruses carry negatively charged envelopes, enabling vdW interfaces particularly positively charged LDH nanosheets—to act as electrostatic viral traps. LDH surfaces can bind virions, adsorb viral proteins, or destabilize the viral envelope via charge imbalance. These interactions have been applied in mucosal formulations and inhalable powders designed to reduce viral load in the respiratory tract, where interlayer flexibility and large surface area maximize pathogen capture.

Catalytic and Redox-Mediated Antiviral Activity

2D MOFs, TMDs, MXenes, and N-doped graphene derivatives can operate as nanozymes, generating ROS in a controlled manner to disrupt viral envelopes or genomes. Such catalytic antiviral coatings offer broad-spectrum activity and can be engineered with self-limiting redox behavior to prevent tissue damage. vdW stacking enables complementary redox layers—such as ROS-generating MOFs and ROS-scavenging LDHs—to be combined strategically for inflammation-balanced antiviral therapy.

Nucleic Acid Delivery and Viral Gene Silencing

LDHs are uniquely suited for the delivery of antiviral siRNA, mRNA, antisense oligonucleotides, or CRISPR components due to their anion-exchange galleries and protection against nuclease degradation. MXene or GO layers can be added to improve cell uptake, enable pH-responsive release, or integrate imaging and photothermal triggers. Such vdW gene-delivery hybrids hold promise for targeting intracellular viral reservoirs, including HIV latency, hepatitis B cccDNA, or persistent post-viral inflammation (eg, long COVID).

Biomimetic and Barrier-Protective Antiviral Coatings

Surface-functionalized vdW nanosheets coated with mucins, pulmonary surfactants, or lipid bilayers can mimic airway or mucosal barriers, altering viral adhesion and enhancing innate immunity. These biomimetic hybrids offer new strategies for topical antivirals, including nasal sprays, lung-directed formulations, and wound-site viral control.

Toward Broad-Spectrum and Pandemic-Ready Antivirals

vdW nanohybrids can be engineered for broad-spectrum antiviral (BSA) logic, combining photothermal decontamination, catalytic virion instability, and targeted gene modulation. Their modularity aligns with pandemic preparedness frameworks: rapid reconfigurability allows adaptation to new viruses, while layered architectures permit simultaneous prophylactic, therapeutic, and barrier functions. Early work with NIC–LDH, and MXene-based antiviral films highlights the translational potential of vdW architectures in respiratory and mucosal viral diseases. For example, nanoengineered niclosamide was found to have the potential as BSA against many emerging viral diseases.[227]

In sum, antiviral vdW nanohybrids offer a unique opportunity to move beyond monofunctional antivirals toward integrated antiviral–immunomodulatory–mucosal-protective platforms. Their ability to couple physical, chemical, and genetic mechanisms within conformal 2D interfaces positions them as a promising frontier for next-generation antiviral strategies with applications in therapy, prevention, and pandemic response.

BNCT-Oriented Platforms

Recent efforts have extended vdW hybridization into boron neutron capture therapy (BNCT), a modality requiring high tumor-selective accumulation of the isotope ^{10}B. Boron-rich 2D materials—such as hexagonal boron nitride (h-BN) or carborane-functionalized nanosheets—serve as high-capacity boron carriers. When coupled with targeting ligands and

ECM-penetration motifs, these platforms ensure preferential localization of ^{10}B in tumor tissues, enabling selective neutron-triggered cytotoxicity. vdW stacking further allows co-loading of radiosensitizers or immunoadjuvants, transforming BNCT from a purely radiological treatment into a multimodal, immune-activating therapeutic strategy.

Together, these applications illustrate the vast biomedical versatility of vdW nanohybrids. Their structural tunability and synergistic layer interactions enable simultaneous imaging, therapy, sensing, and modulation redefining the concept of a single-function nanomaterial. As fabrication precision and biological integration continue to advance, vdW architectures stand poised to become a cornerstone of next-generation intelligent nanomedicine, where diagnosis, therapy, and regeneration converge within a unified, responsive platform.

2D vdW materials are emerging as next-generation boron delivery vehicles for BNCT, exemplified by boron nitride–doped nano-graphene (BNNG). In this system, BNNG is synthesized via CVD to produce 2D boron–nitrogen co-doped graphene sheets with exceptionally high boron loading (~25%), far surpassing BPA's ~5% content. The resulting BN nanosheets grown on GO form an onion-like vdW heterostructure, and subsequent π–π association with PPEG yields water-dispersible BNNG@PPEG suitable for therapeutic applications. As a multifunctional vdW nanoplatform, BNNG@PPEG supports BNCT, chemotherapy, and photothermal therapy, achieving a photothermal conversion efficiency of 40.55% and inducing rapid tumor cell ablation under NIR irradiation. Thermal responsiveness further enables controlled DOX release, while ^{10}B-enriched BNNG generates potent cytotoxicity upon neutron capture, reducing cell viability to ~35%. These results highlight BNNG@PPEG as a potent vdW boron-rich nanosheet hybrid that addresses the limitations of BPA and expands the scope of multifunctional BNCT agents.[228]

Safety, Pharmacology, and Biodegradation

Ensuring the biosafety and pharmacological predictability of vdW nanohybrids is fundamental to their clinical translation.[229] While their multifunctionality and modular design confer therapeutic versatility, these same structural complexities introduce new variables in biocompatibility, immune response, and metabolic clearance. A systematic understanding of hemocompatibility, immune profiling, pharmacokinetics, genotoxicity, and environmental safety is therefore essential to guide responsible development and regulatory acceptance of vdW-based biomedical systems.

An important but often underappreciated factor in the biomedical translation of vdW nanomaterials is the variability of their degradation kinetics in biological environments. The rate at which nanosheets degrade can depend strongly on factors such as layer thickness, defect density, oxidation state, surface functionalization, and environmental conditions including pH, ionic strength, and enzymatic activity. In physiological systems, such variability can influence ion release profiles, biodistribution, and long-term clearance pathways. Materials that degrade too rapidly may lose therapeutic functionality prematurely, whereas excessively stable nanosheets may accumulate in tissues and raise concerns regarding long-term toxicity. Therefore, systematic studies of degradation pathways, metabolic fate, and in vivo clearance are essential to establish reliable safety profiles and guide the design of clinically translatable vdW nanomaterials.

Hemocompatibility and Immune Profiling

The first interface encountered by any intravenously administered vdW nanohybrid is the bloodstream, where plasma proteins, erythrocytes, and immune cells collectively define its biological fate. Rigorous hemocompatibility testing is thus imperative evaluating hemolysis (acceptable limits <5%), complement activation, and platelet aggregation to ensure vascular safety. The unique aspect ratios and edge structures of 2D materials can induce mechanical membrane disruption or oxidative stress; these risks can be mitigated by polymer capping, PEGylation, or biomembrane cloaking, which smoothen surface irregularities and suppress nonspecific adsorption.

Equally critical is the immune response characterization, which distinguishes between "immune-silent" stealth designs and "immune-educating" platforms. Stealth architectures employing PEG or zwitterionic coatings aim to minimize recognition by the mononuclear phagocyte system (MPS) and extend systemic circulation. In contrast, emerging immune-educating nanohybrids deliberately incorporate pathogen-mimetic surface patterns or cytokine-mimic motifs to prime dendritic cells and T-cell responses, particularly in cancer immunotherapy. The ability to toggle between immune evasion and immune activation through surface engineering underscores the adaptive potential of vdW materials in precision immunomodulation.

ADME: Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics of vdW nanohybrids are governed by their lateral dimensions, thickness, charge, and degradability. Nanosheets with lateral sizes below ~100 nm demonstrate superior tumor penetration through enhanced permeability and retention (EPR) effects and can achieve partial renal clearance when their thickness approaches the monolayer regime.[230] In contrast, larger stacks or multi-layered hybrids primarily undergo hepatic sequestration and biliary excretion, reflecting their tendency to form stable protein coronas and accumulate in the reticuloendothelial system (RES).

Biodegradation pathways are material-specific yet predictable. For example, BP degrades into phosphate ions that enter normal metabolic cycles and are eliminated renally. On the other hand, LDHs dissolve into benign cations such as Mg^{2+}, Zn^{2+}, or Al^{3+}, maintaining systemic ion homeostasis. Also, MXenes, particularly Ti_3C_2Tx, gradually oxidize to TiO_2-like phases that are largely inert but may persist depending on surface passivation. GO and rGO undergo enzymatic oxidation via peroxidases (eg, myeloperoxidase), leading to fragmentation into low-molecular-weight carbon species. Importantly, the protein corona's dynamic evolution in vivo alters biodistribution and targeting efficacy. Strategies such as pre-conditioning nanohybrids with selected sera or employing corona-shielding coatings have been shown to stabilize pharmacokinetic profiles and reduce off-target accumulation.

Genotoxicity and Long-Term Fate

Given their prolonged residence in tissues and potential to generate ROS or interact with genomic material, vdW nanohybrids must undergo comprehensive genotoxicity and chronic exposure testing. γ-H2AX phosphorylation and comet assays are standard tools for detecting DNA strand breaks and repair responses. Organ-level retention should be quantified using inductively coupled plasma mass spectrometry (ICP-MS) for metallic elements (eg, Ti, Zn, Mg) and ^{31}P nuclear magnetic resonance (NMR) to monitor BP degradation products. Chronic dosing studies, particularly for regenerative or oncological indications, should also encompass reproductive and developmental toxicity endpoints, as systemic accumulation and transgenerational effects remain insufficiently characterized. Such evaluations will be pivotal in establishing safety margins, dosage ceilings, and re-administration intervals.

Environmental, Health, and Safety (EHS) Considerations

Sustainable synthesis and responsible manufacturing are increasingly recognized as critical components of nanomedicine development. vdW nanohybrid fabrication should prioritize green and aqueous exfoliation techniques, minimize hazardous reagents, and incorporate etchant recovery systems for MXene production to reduce fluoride waste. Adopting low-fluoride or fluoride-free processes mitigates environmental hazards while improving batch reproducibility. Industrial-scale implementation demands closed-loop manufacturing pipelines with stringent endotoxin control, verified by Limulus Amebocyte Lysate (LAL) testing, to ensure pyrogen-free products compliant with GMP standards. Lifecycle analyses encompassing environmental persistence, nanoparticle shedding, and waste management are likewise essential to align vdW nanomedicine with global sustainability goals.

Collectively, these considerations define the safety and pharmacological framework for vdW nanohybrids. Their unique degradability profiles, tunable immune interactions, and responsive pharmacokinetics offer opportunities for rational safety-by-design approaches. However, achieving clinical translation will require harmonizing nanomaterial characterization, biological testing, and regulatory evaluation bridging the gap between sophisticated nanoscale design and the rigorous standards of biomedical safety and environmental stewardship.

Manufacturing and Regulatory Translation

The successful translation of vdW nanohybrids from laboratory innovation to clinical application hinges on the establishment of robust, scalable, and regulatory-compliant manufacturing pipelines. While these layered architectures offer extraordinary design versatility, their structural complexity also poses challenges for reproducibility, quality control, and long-term stability. Translational success therefore, depends on integrating advanced processing methods, precise material characterization, and harmonized regulatory frameworks tailored to hybrid nanomaterials.

Scale-Up and Process Control

Scaling the synthesis of vdW nanohybrids requires maintaining control over both in-plane dimensions and interlayer attributes, as these directly affect biological behavior and therapeutic performance. Modern shear-mixing and microfluidic exfoliation technologies enable reproducible production of monolayer or few-layer nanosheets with uniform lateral size distribution, while minimizing oxidation and mechanical defects. For multilayer assemblies, roll-to-roll layer-by-layer deposition offers an efficient route to fabricate thin films or patch-based devices with consistent stacking order and composition. Similarly, spray coating and inkjet printing methods are increasingly employed to produce conformal vdW coatings for wearable electronics and biointegrated sensors.

Defining and monitoring Critical Quality Attributes (CQAs) is essential for regulatory acceptance and product consistency. These include thickness uniformity, oxidation state, surface terminations (particularly for MXenes), interlayer spacing (in LDHs and MOFs), zeta potential, and the absence of residual reagents or etchants. Endotoxin content must be strictly controlled, given the sensitivity of biological systems to pyrogenic contaminants. Inline analytical tools such as Raman spectroscopy, XPS, and dynamic light scattering can support process analytics and real-time quality monitoring, enabling a transition towardGMP-compliant production.

Formulation and Stability Engineering

The colloidal and chemical stability of vdW nanohybrids determines their clinical shelf life and pharmacological reliability. Lyophilization (freeze-drying) is the preferred approach for long-term storage, often combined with cryoprotectants such as trehalose or mannitol to preserve nanosheet integrity and prevent aggregation during rehydration. For oxidation-sensitive materials such as BP and MXenes, the inclusion of oxygen scavengers or inert-gas packaging substantially prolongs stability.

Ensuring sterility remains another crucial step. While 0.22 μm filtration is suitable for smaller colloids, larger or lamellar systems may require gamma or electron-beam sterilization following compatibility testing to confirm structural and functional preservation. For hydrogels, wound dressings, and implantable composites, aseptic assembly under controlled environments may offer a safer alternative to post-synthesis sterilization. Stability testing should follow International Council for Harmonisation (ICH) guidelines, including stress studies under varying temperature, humidity, and light exposure to ensure physicochemical consistency across the product lifecycle.

Regulatory Pathways and Clinical Integration

The regulatory classification of vdW nanohybrids depends on their intended use and mechanism of action, often positioning them within hybrid frameworks that merge aspects of drugs, biologics, and devices. Drug–device combination products, such as wound dressings or implantable patches, typically follow medical device routes supplemented with drug-eluting guidance under agencies like the FDA's Center for Devices and Radiological Health (CDRH) or the EMA's Medical Device Regulation (MDR).

For theranostic injectables and targeted nanomedicines, regulatory oversight aligns more closely with small-molecule or biologic Chemistry, Manufacturing, and Controls (CMC) standards, augmented by evolving nanomaterial-specific guidance addressing characterization, safety, and environmental impact. Process changes such as modifications in exfoliation method, surfactant chemistry, or sterilization technique must be supported by rigorous comparability studies demonstrating unchanged physicochemical and biological performance.

To support precision and safety in photo-responsive or electroactive nanotherapies, the integration of companion diagnostics is increasingly encouraged. Real-time dosimetry, light-fluence mapping, or impedance monitoring systems provide quantitative control over exposure parameters, strengthening the risk–benefit profile in regulatory dossiers. This convergence of material and device data within a unified regulatory submission reflects the shift toward evidence-based approval pathways for multifunctional nanotherapeutics.

In summary, the translation of vdW nanohybrids into clinical-grade materials demands not only chemical and biological sophistication but also manufacturing discipline and regulatory foresight. Scalable synthesis, reproducible quality metrics, and transparent safety validation form the triad that will define their path from academic discovery to

industrial deployment. As standards evolve to accommodate hybrid nanoplatforms, vdW architectures stand poised to become leading exemplars in the era of integrated, intelligent, and clinically actionable nanomedicine.

Design Rules of Thumb: A Translational Blueprint for vdW Nanohybrids

Bridging the conceptual sophistication of vdW nanohybrids with clinical utility requires a practical playbook that unites mechanism, interface engineering, safety, synergy, and scalability. The following unified design philosophy distills actionable principles from across preclinical and translational evidence, offering researchers a coherent roadmap from benchtop innovation to bedside impact.

First, match mechanism to indication. Biomedical challenges are highly context-specific, and the choice of 2D substrate should be mechanistically aligned with the disease niche. NIR-II-active MXenes and BP are best suited for deep-seated tumors where photothermal penetration is critical; LDHs can co-deliver siRNA targeting survival pathways such as STAT3 or HIF-1α to enhance cytotoxicity. Catalytic–photothermal TMD/MXene hybrids paired with Zn- or Mg-LDHs are optimal for biofilms and chronic wounds, where matrix disruption and regeneration must occur simultaneously. In neurointerfaces, MXene/graphene laminates embedded in soft hydrogels should maintain an impedance below 10 kΩ at 1 kHz to enable precise electrophysiological coupling.

Second, engineer the interface first. In biological systems, the surface not the core material dictates fate. Hydrodynamic sizes of 50–120 nm with near-neutral zeta potentials (−10 to +5 mV) balance circulation, tissue penetration, and reduced opsonization. Surface chemistry should be designed with protein corona logic in mind, using PEG, zwitterionic polymers, or biomembrane cloaks not only to suppress unwanted interactions but also to tune immune engagement and biodistribution intentionally.

Third, build safety in from the start. Biodegradability and self-passivation must be intrinsic features. BP and LDH naturally degrade into biocompatible ions, while MXenes should be engineered with controlled oxide shells to prevent uncontrolled reactivity. Heavy-metal leaching should be avoided, and antioxidant stabilizers selected to mitigate oxidative degradation. Safety-by-design approaches must harmonize with ISO 10993 biocompatibility expectations and emerging nano-specific regulatory frameworks.

Fourth, exploit vdW complementarity. The true power of vdW nanohybrids lies in rational stacking of complementary functions. Photothermal absorbers (MXene/BP) can be paired with catalytic or oxygen-evolving 2D MOFs, buffering LDHs, or ECM-modulating layers to achieve coordinated photonic, redox, and biochemical activity. Intelligent pairing ensures synergy deep-tissue penetration, ROS regulation, immune activation, and ECM normalization rather than functional interference.

Finally, plan for translation from day one. Scalable synthesis, reproducibility, and regulatory foresight must be embedded early. Water-based, surfactant-light exfoliation and pharmaceutically traceable reagents are preferred. Critical Quality Attributes (CQAs) including layer thickness, oxidation state, and interlayer spacing should be defined upfront, alongside stability-indicating assays for both powder and suspension forms. Compatibility with standard sterilization methods (filtration, gamma, or e-beam) should be established before preclinical expansion.

Together, these principles form a translation-oriented design doctrine for vdW nanohybrids aligning mechanistic rationale, interfacial precision, intrinsic safety, synergistic architecture, and manufacturability (Figure 6). The next generation of vdW biomedical platforms will be judged not only by atomic-scale ingenuity, but by how seamlessly they integrate into clinically credible, scalable, and ethically responsible therapeutic ecosystems.

Outlook and Outstanding Questions

As vdW nanohybrids mature from conceptual prototypes to translationally viable systems, their next frontier lies in bridging biological intelligence with material logic. The coming decade will likely witness the emergence of adaptive, self-regulating, and ethically sustainable 2D therapeutics, yet several fundamental questions remain unanswered. Addressing these challenges will determine how far vdW nanohybrids can evolve from multifunctional tools to truly integrative biomedical technologies.

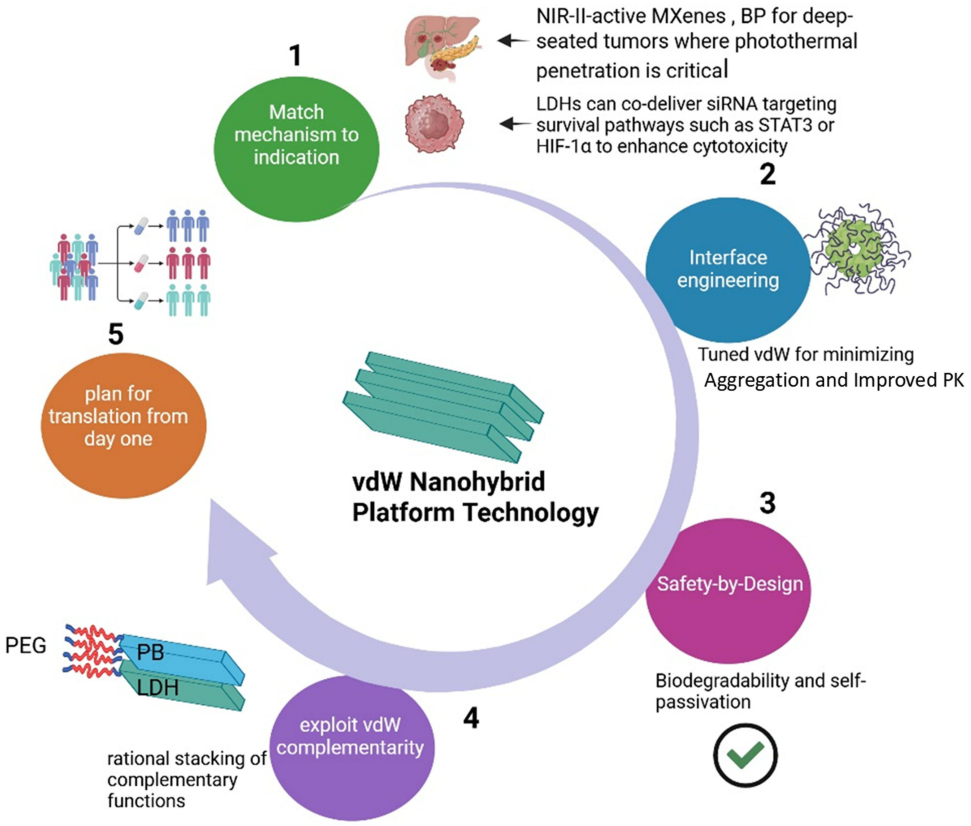

Figure 6 Translational Design Blueprint for 2D vdW Nanohybrids. A unified framework outlining five actionable design principles for clinically oriented vdW nanohybrid development. (1) Match mechanism to indication: Select 2D materials based on disease-specific requirements, such as NIR-II-active MXenes or black phosphorus for deep-seated tumors, and LDHs for siRNA co-delivery to suppress survival pathways (eg, STAT3, HIF-1α). (2) Interface engineering: Optimize vdW surfaces and coatings to minimize aggregation, modulate protein Corona behavior, and improve pharmacokinetics. (3) Safety-by-Design: Incorporate intrinsic biodegradability and controlled self-passivation to ensure safe material clearance. (4) Exploit vdW complementarity: Rationally stack complementary 2D layers (eg, LDH, photothermal sheets, PEG) to integrate photonic, catalytic, and biochemical functions. (5) Plan for translation from day one: Embed manufacturability, scalability, and regulatory foresight early in design. Together, these principles guide the evolution of vdW nanohybrids from atomic-scale engineering toward clinically credible platform technologies (Figure was made by Biorender.com).

Mechano-Immuno-Hybrids

Can vdW architectures be designed to sense and respond to biomechanical cues within the tumor microenvironment? Desmoplastic cancers and fibrotic tissues present stiff, immunosuppressive niches that currently resist therapeutic penetration. Engineering mechanoresponsive vdW hybrids capable of detecting ECM stiffness and releasing immunostimulants or checkpoint inhibitors only in such zones could transform local mechanical resistance into a biological trigger for immune activation. Integrating mechano-sensing elements with immune payloads may redefine the interface between mechanobiology and immunotherapy.

Closed-Loop Bioelectronics

Will conductive 2D nanohybrids enable autonomous, closed-loop therapeutic systems that can sense, compute, and deliver interventions in real time? The high conductivity, flexibility, and biocompatibility of MXene- or graphene-based stacks make them ideal candidates for wearable or implantable patches capable of detecting electrophysiological anomalies such as arrhythmia, epileptic discharges, or inflammatory signatures and autonomously delivering electrical or drug-based corrective responses. Realizing such bioelectronic reflexes would bridge diagnostics, therapy, and computation in a single bio-integrated platform.

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BNCT Convergence

Can boron-rich 2D hybrids enable a new paradigm in cancer therapy by merging boron neutron capture therapy (BNCT) with in situ immunomodulation? vdW assemblies incorporating h-BN, carborane clusters, or boronated MOFs could concentrate ^{10}B within tumors while co-delivering immune adjuvants or gene silencers. This integration might transform BNCT from a purely radiological intervention into a systemic anti-tumor immunotherapy, capable of inducing abscopal effects and long-term immune memory.

Regulatory Harmonization

Despite rapid advances, the regulatory landscape for 2D nanohybrids remains fragmented and largely reactive. There is a pressing need for standardized reference materials, validated assays, and cross-family toxicity databases that can accurately predict long-term biodistribution, degradation, and immunogenicity. Establishing international consensus through organizations such as ISO, OECD, and WHO will be essential to build confidence among regulators and accelerate the safe adoption of vdW nanomedicine.

Manufacturing Equity

Finally, the promise of vdW nanohybrids must extend beyond academic laboratories to global healthcare systems. Can green, low-cost exfoliation and scalable printing techniques democratize access to 2D therapeutics and diagnostics, particularly in low-resource settings? Developing aqueous, solvent-free, and energy-efficient production lines not only reduces environmental burden but also ensures equitable access to next-generation medical technologies; a key ethical imperative in the future of nanomedicine.

In essence, the next era of vdW nanohybrids will be defined not only by advances in atomic precision but by systems-level integration—mechanical, electronic, immunological, and societal. Their evolution into adaptive, self-aware biomedical systems will depend on the convergence of materials science, synthetic biology, bioelectronics, and policy. Answering these outstanding questions will transform vdW nanohybrids from a technological curiosity into a cornerstone of intelligent, inclusive, and sustainable nanomedicine.

Recent literature underscores the rapid evolution of vdW nanohybrid science into the biomedical domain. For example, MXene-based composites have matured into multifunctional scaffolds and coatings tailored for drug delivery, tissue growth and sensor integration. Simultaneously, biomimetic and biomodified 2D hybrids are increasingly harnessed for ultrasensitive biosensing via peptide/oligonucleotide surface anchoring. The sensing horizon is further expanded by heterostructures capable of responding to multiple stimuli (mechanical, optical, chemical) through layered 2D architecture. In tandem, advances in precision nanofabrication—such as femtosecond laser ablation of vdW sheets bring the promise of size, geometry and defect control necessary for biomedical translation (eg, clearance, biodistribution, loading). Altogether, these developments validate the central premise of this review: that modular vdW assembly + surface engineering + functional layering is enabling a new class of biomedical nanomaterials.

Translational Pipeline for vdW Nanohybrids

The path from vdW nanohybrid concept to clinical reality is necessarily stepwise, iterative, and indication-specific. A pragmatic translational pipeline for 2D vdW systems can be envisioned in six interlocking stages.

Mechanism–Indication Mapping and Materials Triage

Discovery begins with aligning a vdW architecture to a clearly defined clinical problem: photothermal–chemo–gene stacks for refractory solid tumors, immunomodulatory LDHs for autoimmune disease, or conductive MXene/graphene laminates for bioelectronic neuromodulation. At this stage, material libraries are filtered based on basic physicochemical metrics—layer thickness, oxidation state, dispersibility, surface charge, and degradability—as well as in vitro readouts of function (drug loading, nanozyme activity, photothermal efficiency, electrophysiological performance).

Interfacial Optimization and Biological Identity

Promising candidates then undergo systematic surface engineering to shape the biological corona and in vivo fate. PEG, zwitterionic polymers, biomembrane cloaks, and targeting ligands (eg, RGD, folate, antibodies) are screened for effects on protein adsorption, complement activation, macrophage uptake, and biodistribution. This "interface-first" optimization is particularly critical for 2D materials, whose extreme aspect ratio makes their surface chemistry the dominant determinant of safety and efficacy.

Preclinical Safety-by-Design

Before moving toward first-in-human studies, vdW candidates must satisfy nano-specific safety criteria beyond classical cytotoxicity. These include hemocompatibility, genotoxicity, immunogenicity, thrombosis/embolism risk, long-term organ retention, and degradant profiling. Human inhalation exposure to graphene oxide nanosheets, for example, has already been explored in a controlled volunteer study to probe acute pulmonary and cardiovascular responses, demonstrating short-term tolerability at low aerosolized doses.[231] Similar safety-by-design frameworks will be required for other vdW families such as MXenes, LDHs, and boron nitride hybrids before systemic administration can be justified.

Manufacturability, Quality, and Regulatory Alignment

In parallel, synthesis routes must be adapted to GMP-compatible, scalable processes ideally aqueous, surfactant-lean exfoliation or bottom-up growth that minimize residual reagents. Critical Quality Attributes (CQAs) such as lateral size distribution, layer number, oxidation state, interlayer spacing, residual metal content, and endotoxin burden must be defined and controlled with validated assays. Regulatory positioning (drug, device, or combination product) determines whether ICH/EMA small-molecule biologics guidance or device standards (eg, ISO 10993) are primary; most early vdW entries such as wound dressings, periodontal graft adjuncts, or neural recording interfaces currently follow the medical-device pathway.

Early Clinical Prototypes in "Low-Risk" Indications

Initial human use of vdW materials has clustered around applications where exposure is local, controllable, and reversible. Examples include graphene oxide as an adjunct in periodontal surgery for intrabony defects (NCT05341245), graphene-reinforced PMMA dentures for improved mechanical performance (NCT06856239), and graphene cortical electrodes for intra-operative brain mapping in glioma surgery (NCT06368310). In parallel, graphene-based far-infrared textiles have been tested as non-invasive interventions for mood and cognitive symptoms in older adults,[232] and nitrogen/sulfur-doped graphene quantum dot biosensors for breast-cancer detection are now entering early clinical evaluation (NCT07034248). These device-oriented trials provide invaluable real-world data on biocompatibility, handling, and user integration.

Expansion to Systemic Therapies and Intelligent Platforms

The longer-term horizon is the deployment of vdW nanohybrids as systemic drugs or "intelligent" therapeutic platforms chemo–photothermal–gene stacks, boron-rich 2D agents for BNCT, or closed-loop bioelectronic implants based on graphene/MXene laminates. At present, MXene- and LDH-based platforms remain in the preclinical domain despite rapidly expanding in vivo datasets for wound healing, cancer therapy, and immunomodulation.[233] A deliberate progression from local device use to controlled systemic exposure, accompanied by harmonized international guidelines and shared toxicity databases, will be essential to avoid repeating past nanomedicine bottlenecks.

Together, this translational pipeline (Table 6) emphasizes that vdW nanohybrids will reach the clinic not merely by virtue of their atomic-scale sophistication, but through coordinated advances in interfacial design, safety-by-design, scalable manufacturing, and indication-matched clinical strategy.

Table 6 Current and Emerging Clinical Trials Involving vdW-Type 2D Materials

#	vdW Material/ Configuration	Clinical Indication/Use	Trial Type and Phase	Identifier/ Reference	Notes & vdW Category
1	Graphene oxide nanosheets in periodontal defects	Regenerative treatment of intrabony periodontal defects during flap surgery	Interventional, randomized experimental study (treatment)	NCT05341245	GO applied as a regenerative adjunct within bony defects; local vdW 2D sheet used as scaffold/biomodifier.
2	Graphene cortical interface (INBRAIN)	Intra-operative brain mapping during glioma/brain-tumor surgery	First-in-human device study, interventional; safety and signal-quality endpoints	NCT06368310	Ultrathin graphene-based flexible electrodes (2D conductor) placed on cortex; vdW heterostructure with parylene substrate.
3	N,S-doped graphene quantum dots on Au nanoparticles (NSGQD/ AuNP biosensor)	Electrochemical detection of breast-cancer cells in clinical samples	Early clinical diagnostic study (Phase 1/4)	NCT07034248	vdW-type nanohybrid combining graphene QDs with AuNPs on an electrode; aims to translate lab biosensor to clinical diagnostics.
4	Graphene-reinforced PMMA denture base	Evaluation of mechanical performance of complete dentures	In-vitro / clinical materials study (Not Applicable phase)	NCT06856239	PMMA reinforced with graphene filler; primarily mechanical/structural outcome but represents a vdW composite entering dental practice.
5	Graphene far-infrared textile (GFII)	Non-invasive intervention for depression, anxiety, and cognitive impairment in older adults	Randomized controlled trial	[232]	Wearable textile incorporating graphene to generate far-infrared radiation; demonstrates 2D-enabled device-level therapy.
6	Inhaled thin graphene oxide nanosheets	Safety assessment of acute inhalation exposure in healthy volunteers	Double-blind, randomized, controlled human exposure study	Nature Nanotechnology 2024[231]	First controlled human inhalation trial of graphene oxide; not therapeutic but critical for risk assessment of airborne 2D materials.

Notes: As of 2025, clinical translation of other vdW families such as MXenes, LDHs, and boron nitride nanosheets remains confined to preclinical models, despite extensive evidence for their potential in cancer therapy, wound repair, immunomodulation and BNCT.176 These platforms represent the next wave of candidates expected to enter early-phase clinical studies once safety, manufacturing, and regulatory hurdles are addressed.

Future Prospect

Over the past decade, vdW nanohybrids have evolved from conceptual 2D assemblies into a versatile platform for multifunctional biomedical innovation. Their defining characteristic the modular stacking of atomically thin layers through weak interfacial forces, has unlocked a new dimension in materials design, where distinct optical, electronic, catalytic, and mechanical functionalities can be integrated without compromising structural integrity. This architectural flexibility has allowed the creation of layer-engineered systems that mimic biological logic, performing sensing, computation, and therapy within a single construct.

In the biomedical context, vdW nanohybrids transcend the limitations of isotropic nanoparticles by offering tunable anisotropy, high surface accessibility, and programmable interlayer interactions. From MXene- and BP-based photothermal agents to LDH- and MOF-derived catalytic and gene-delivery platforms, these materials demonstrate remarkable synergy capable of harvesting light, modulating redox states, releasing therapeutic cargo, and even engaging the immune system. Their biological adaptability extends beyond therapy: conductive and flexible vdW laminates are now enabling neural interfaces, cardiac patches, and wearable biosensors that blur the boundary between electronics and living tissue.

Yet, translating this promise into clinical reality requires a holistic understanding of the structure–property–biology nexus. The same properties that confer high functionality reactivity, conductivity, and ultrathin geometry also demand careful regulation to ensure biosafety, reproducibility, and long-term stability. Recent progress in polymer and biomembrane functionalization, controlled degradation pathways, and protein corona engineering illustrates how rational interface design can harmonize synthetic precision with biological complexity. Complementary advances in microfluidic exfoliation, inkjet printing, and GMP-compliant roll-to-roll assembly are laying the groundwork for scalable and standardized production.

Looking forward, the next wave of vdW biomedical materials will move from multifunctionality toward adaptive intelligence systems capable of self-sensing, self-regulation, and contextual therapeutic decision-making. Emerging

directions include mechano-immuno hybrids that couple stiffness sensing with immune activation, closed-loop bioelectronics integrating sense–compute–deliver cycles for real-time therapy, and boron-rich 2D constructs that unite BNCT with in situ vaccination. Parallel to these scientific advances, regulatory harmonization, green manufacturing, and equitable deployment will determine how widely and responsibly these technologies are adopted.

In summary, vdW nanohybrids represent more than an incremental advance in nanomaterial science; they embody a paradigm shift toward intelligent, integrative, and ethically conscious nanomedicine. By uniting atomic precision with biological responsiveness, they redefine how matter interacts with life. The challenge now lies not in proving what these materials can do, but in engineering them to do so safely, reproducibly, and inclusively transforming vdW nanohybrids from laboratory ingenuity into a new foundation for global health innovation.

Conclusions

Van der Waals (vdW) nanohybrids represent a rapidly emerging class of materials that combine the structural precision of two-dimensional (2D) systems with the functional diversity of hybrid nanostructures. As highlighted throughout this review, the modular stacking of atomically thin layers through weak interfacial interactions enables the integration of distinct optical, electronic, catalytic, and mechanical properties without disrupting the intrinsic lattice structures of individual components. This unique assembly principle has led to the development of a wide spectrum of vdW hybrid architectures, including graphene-, MXene-, LDH-, TMD-, MOF-, and polymer-based nanosheets.

These materials have demonstrated remarkable potential across diverse biomedical applications. Their high surface accessibility, tunable interlayer spacing, and programmable interface chemistry allow vdW nanohybrids to function as multifunctional platforms capable of photothermal therapy, catalytic redox modulation, drug and gene delivery, biosensing, and bioelectronic interfacing. In addition, the anisotropic structure of vdW systems enables efficient energy transfer, charge separation, and molecular recognition processes that are difficult to achieve with conventional isotropic nanomaterials.

Importantly, vdW hybrid materials also offer unprecedented opportunities for integrating biological functionality with electronic and catalytic properties. Flexible and conductive vdW laminates are enabling new generations of neural interfaces, wearable biosensors, and responsive therapeutic platforms that closely interact with biological systems. These advances highlight the transformative potential of vdW nanohybrids as a unifying framework for designing multifunctional nanomaterials at the interface of chemistry, materials science, and biomedicine.

Overall, vdW nanohybrids provide a powerful materials paradigm for constructing modular, multifunctional systems with precisely engineered interfaces. Continued advances in synthesis, structural control, and biological integration will further expand their impact across nanomedicine, bioelectronics, and translational biomedical technologies.

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Disclosure

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