

Two-Dimensional Materials Beyond Graphene for Biomedical and Healthcare Applications: Transition Metal Dichalcogenides, MXenes, Black Phosphorus, Xenes, Biosensors and Wearable Health Monitoring Platforms

Safdar Abbas

Department of Physics, Government Graduate College Jaranwala, Punjab, Pakistan

Faizan Azmat (Corresponding Author)

Department of Physics, Government Graduate College Jaranwala, Punjab, Pakistan
sheikhfaizanofficial@outlook.com

Ali Murtaza

Department of Physics, Government Graduate College Jaranwala, Punjab, Pakistan

Ali Shabaz

Department of Physics, Government Graduate College Jaranwala, Punjab, Pakistan

Samra Ashfaq

Department of Physics, Government Graduate College Jaranwala, Punjab, Pakistan

ABSTRACT

The isolation of graphene in 2004 initiated a rapidly expanding field of two-dimensional (2D) materials, many of which now offer biomedical functions that graphene alone cannot provide. Beyond graphene, transition metal dichalcogenides (TMDs), MXenes, black phosphorus (BP), Xenes, and hexagonal boron nitride (h-BN) possess tunable electronic structures, strong near-infrared (NIR) optical absorption, large surface-to-volume ratios, flexible mechanical behavior, and diverse surface chemistries. These properties make them promising candidates for drug delivery, photothermal and photodynamic therapy, bioimaging, tissue engineering, neural interfaces, field-effect transistor (FET) biosensors, and wearable or implantable health monitoring systems.

This review provides a unified assessment of 2D materials beyond graphene for biomedical and healthcare applications. We evaluate TMDs such as MoS₂, WS₂, and MoSe₂ for cancer drug delivery, photothermal therapy, multimodal imaging, and gene delivery. MXenes, particularly Ti₃C₂T_x and Nb₂CT_x, are reviewed for photothermal therapy, antibacterial coatings, immunotherapy, electrochemical biosensing, and next-generation neural interfaces. Black phosphorus is examined as a biodegradable theranostic and tissue-regenerative material, while Xenes including antimonene, bismuthene, borophene, and h-BN are discussed for phototherapy, CT imaging, biosensing, drug delivery, and boron neutron capture therapy (BNCT). Finally, we

Online ISSN

3007-3197

Print ISSN

3007-3189

<http://amresearchreview.com/index.php/Journal/about>

critically assess biocompatibility, toxicology, biodegradability, scalability, regulatory pathways, and clinical translation readiness.

Although no 2D material beyond graphene has yet reached routine clinical use, several systems including MXene neural electrodes, MoS₂ FET biosensors, BP-based biodegradable scaffolds, and borophene biosensors have reached advanced preclinical or high-performance prototype stages. We conclude that the future of 2D biomaterials will depend less on achieving isolated performance records and more on reproducible manufacturing, long-term safety validation, clinically relevant testing, and regulatory alignment.

Keywords— two-dimensional materials; transition metal dichalcogenides; MXenes; black phosphorus; Xenes; photothermal therapy; drug delivery; biosensors; neural interfaces; wearable electronics; clinical translation.

Highlights

- TMDs, MXenes, black phosphorus, and Xenes offer distinct and complementary biomedical properties unavailable in graphene alone.
- MoS₂ FET biosensors achieve femtomolar-to-attomolar sensitivity for cancer, cardiac, and infectious disease biomarkers.
- Ti₃C₂T_x MXene neural electrodes demonstrate approximately 30–100-fold lower impedance than conventional Pt/Ir electrodes of matched area and superior chronic recording stability.
- Black phosphorus degrades into biocompatible phosphate species (HPO₄²⁻ and H₂PO₄⁻ at physiological pH), enabling self-eliminating theranostic and tissue engineering platforms.
- No non-graphene 2D material has reached clinical use; reproducible manufacturing, long-term safety, and regulatory alignment remain the critical barriers.

1. Introduction: From Graphene to a Universe of 2D Biomaterials

The isolation of monolayer graphene by Novoselov and Geim in 2004 demonstrated that stable atomically thin crystals can exist under ambient conditions [1]. This discovery transformed condensed matter physics, nanotechnology, and materials chemistry. However, graphene is only one member of a much larger family of 2D materials [2, 3]. Within the following decade, researchers identified and synthesized numerous 2D systems, including transition metal dichalcogenides, hexagonal boron nitride, MXenes, black phosphorus, and monoelemental Xenes such as antimonene, bismuthene, silicene, germanene, tellurene, and borophene [4, 5]. Naturally occurring layered minerals such as vermiculite have also been exfoliated into functional 2D nanosheets for biomedical exploration [6].

These materials are not simply graphene alternatives; they offer properties that graphene does not possess. TMDs provide semiconducting bandgaps and strong photoluminescence in the visible range. MXenes combine metallic conductivity with hydrophilic surfaces and rich surface terminations. Black phosphorus offers layer-dependent direct bandgaps and biodegradation into biocompatible phosphate species. h-BN provides electrical insulation and high chemical stability. Xenes offer diverse optical, electronic, and high-atomic-number properties suitable for imaging,

Online ISSN

3007-3197

Print ISSN

3007-3189

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radiotherapy enhancement, and biosensing [7]. The combined portfolio of 2D materials now spans insulators, semiconductors, semimetals, and metals, enabling rational material selection for specific biomedical functions rather than forcing a single material to perform every task.

The biomedical relevance of 2D materials arises from their geometry as much as from their chemistry. Atomically thin nanosheets possess ultrahigh surface-to-volume ratios, allowing high drug loading, dense biomolecule functionalization, and efficient interaction with biological membranes. Their optical properties can be tuned by composition, thickness, and surface chemistry, enabling photothermal therapy, photodynamic therapy, and photoacoustic imaging. Their flexibility and conformability make them attractive for bioelectronic interfaces, including skin-mounted wearables, implantable sensors, and neural electrodes. These geometric and electronic advantages explain why 2D materials have progressed from curiosity-driven physics to a clinically oriented biomedical discipline within roughly two decades.

The clinical need for such technologies is substantial. Cancer remains a leading cause of mortality worldwide; antimicrobial resistance threatens modern medicine; neurological disorders require better brain-machine interfaces; and the COVID-19 pandemic exposed the urgent need for rapid point-of-care diagnostics. 2D materials are uniquely positioned at the interface of therapy, diagnostics, and real-time monitoring. This review focuses on four interconnected biomedical pillars: (i) TMDs for drug delivery, photothermal therapy, gene delivery, and cancer theranostics; (ii) MXenes for photothermal therapy, antibacterial applications, immunotherapy, biosensing, and neural interfaces; (iii) Black phosphorus, Xenes, and h-BN for biodegradable theranostics, tissue engineering, bioimaging, and biosensing; and (iv) 2D material biosensors and wearable/implantable platforms for biomarkers, pathogens, nucleic acids, electrophysiology, and continuous health monitoring.

1.1 Scope, Limitations, and Positioning Relative to Prior Reviews

Several important reviews have addressed subsets of this field. Babar et al. [8] provided a comprehensive account of MXene healthcare applications with emphasis on synthesis and bioimaging. Sun et al. [9] focused specifically on biodegradable black phosphorus biomaterials for cancer and tissue engineering. Liu et al. [10] surveyed TMD biomedical applications with broad coverage of functionalization strategies, while Nisar et al. [11] assessed 2D material electronic biosensors for point-of-care diagnostics. The present review is distinguished from these works in three ways. First, it integrates all major non-graphene 2D material families like TMDs, MXenes, BP, and Xenes including borophene and h-BN within a single unified framework rather than treating each family in isolation. Second, it explicitly connects materials properties to clinical translation metrics, including Technology Readiness Level (TRL) assignment following the NASA TRL scale (NASA NPR 7123.1), regulatory pathway mapping, and a ClinicalTrials.gov landscape analysis current as of the most recent search. Third, it incorporates the most recent developments (2023–2025) in neural interfaces, biodegradable MXenes, borophene biosensing, and AI-assisted signal processing that postdate earlier surveys. The review does not attempt exhaustive coverage of graphene-based systems, which are treated only where direct comparison with non-graphene 2D materials is instructive. Synthesis methods are discussed in the context of biomedical

Online ISSN

3007-3197

Print ISSN

3007-3189

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relevance rather than as an independent topic, and energy storage applications of 2D materials lie outside the scope of this work [12, 13].

Photothermal conversion efficiency (PCE) values cited throughout this review were calculated by the original authors using the time-constant method of Roper et al. (2007) unless otherwise noted. Direct cross-study comparison of PCE values is limited by differences in laser wavelength, irradiance, sample geometry (dispersion vs solid film), thermal isolation method, and the assumed heat-transfer coefficient. PCE values should therefore be interpreted as order-of-magnitude indicators rather than as precise inter-material rankings. Where the original literature reports PCE values using alternative calculation methods, this is noted explicitly.

2. Transition Metal Dichalcogenides for Drug Delivery, Photothermal Therapy and Theranostics

2.1 Structure and Biomedical Properties of TMDs

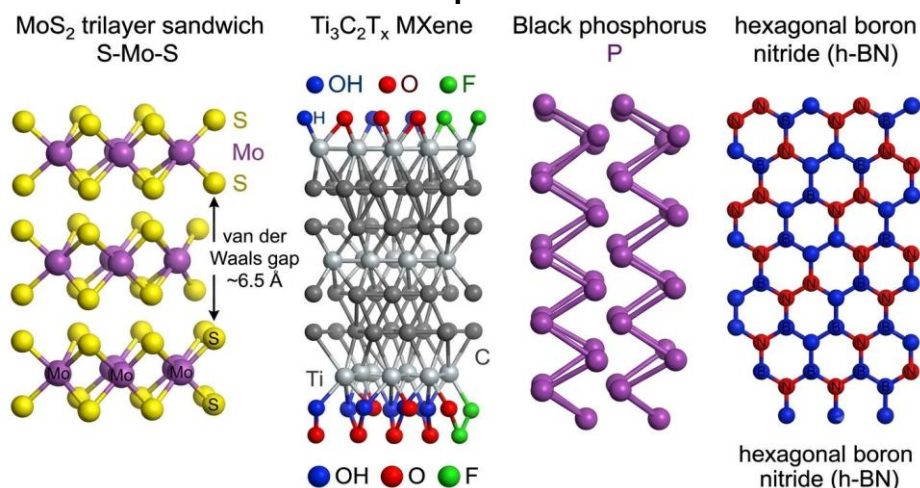


Figure 1. Crystal structures of representative two-dimensional biomedical nanomaterials. (A) MoS₂ transition metal dichalcogenide showing the characteristic S–Mo–S trilayer sandwich structure, with adjacent layers separated by a van der Waals gap of 6.5 Å. (B) Ti₃C₂T_x MXene exhibiting alternating Ti and C atomic layers terminated by hydrophilic surface functional groups (–OH, –O, –F), which confer colloidal stability and enable biomolecule conjugation. (C) Black phosphorus (BP) displaying its puckered honeycomb lattice of phosphorus atoms, the structural basis of its high carrier mobility and biodegradability. (D) Hexagonal boron nitride (h-BN) showing the planar honeycomb arrangement of alternating boron and nitrogen atoms, underlying its chemical inertness and dielectric properties.

Transition metal dichalcogenides have the general formula MX₂, where M is a transition metal such as Mo, W, Nb, or Re, and X is a chalcogen such as S, Se, or Te. The most widely studied biomedical TMDs are MoS₂, WS₂, and MoSe₂. Their crystal structure consists of a transition metal layer sandwiched between two chalcogen layers, with adjacent sheets held together by van der Waals interactions. Solution-processed exfoliation of high-quality 2H-MoS₂ nanoflakes is a well-established route to biomedical-grade material [14]. A defining feature of TMDs is their layer-dependent electronic structure: MoS₂ changes from an indirect bandgap semiconductor in bulk

Online ISSN

3007-3197

Print ISSN

3007-3189

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form (bandgap 1.2 eV) to a direct bandgap semiconductor at the monolayer limit (bandgap 1.8–1.9 eV) [5, 15]. The indirect-to-direct transition at the monolayer limit yields strong photoluminescence in the red/visible range (660–690 nm). Separately, the photothermal therapy (PTT) response of MoS₂ nanosheets under 808 nm irradiation arises from sub-bandgap defect-state and excitonic absorption, not from the band-edge transition; these two optical responses should not be conflated.

The biomedical value of TMDs also comes from large surface area for drug loading and biomolecule conjugation, NIR absorption for photothermal therapy, semiconducting behavior for FET biosensing, surface functionalization via PEG, chitosan, hyaluronic acid, antibodies, and aptamers, and multimodal imaging potential when combined with magnetic, fluorescent, or high-Z components [10]. TMDs can exist in multiple polymorphic phases. The thermodynamically stable 2H phase (trigonal prismatic coordination, space group P6₃/mmc) is semiconducting and most relevant for drug delivery, PTT, and FET biosensing. The metastable 1T phase (octahedral coordination) is metallic and exhibits superior hydrophilicity and electrochemical activity, making it useful for electrochemical biosensing and as a conductive scaffold for composite materials. Phase engineering via chemical intercalation (e.g., *n*-butyllithium) or electron-beam irradiation allows switching between phases, providing an additional handle for tuning biomedical performance [5, 10].

The lateral size and thickness of TMD nanosheets, typically controlled by liquid-phase exfoliation (LPE) or chemical vapor deposition (CVD), strongly influence cellular uptake, blood circulation half-life, biodistribution, and immune recognition. Smaller nanosheets (below 100 nm lateral dimension) generally show more favorable pharmacokinetics for intravenous delivery, while larger sheets may be preferred for topical or implanted scaffold applications. These geometric considerations must be factored into any translational design [10, 16].

2.2 MoS₂ for Drug Delivery and Cancer Therapy

MoS₂ is one of the most extensively studied 2D materials for cancer nanomedicine [17]. Exfoliated MoS₂ nanosheets provide large surface areas and can adsorb therapeutic molecules through π – π stacking, electrostatic interactions, and hydrophobic forces [15]. High-throughput synthesis of single-layer MoS₂ nanosheets as NIR photothermal-triggered drug delivery vehicles has further advanced the field [17]. Doxorubicin (DOX), cisplatin, curcumin [18], and nucleic acids have been loaded onto MoS₂ platforms. Surface modification is essential: PEGylation improves colloidal stability and circulation time; hyaluronic acid enables active targeting toward CD44-overexpressing tumor cells; and chitosan enables pH-responsive drug release. MoS₂-mediated combined chemotherapy and photothermal therapy has shown strong synergistic effects in preclinical cancer models, often achieving greater tumor inhibition than either modality alone.

Quantitative performance benchmarks for MoS₂ drug delivery platforms have been established in the literature. PEGylated MoS₂ nanosheets functionalized with hyaluronic acid achieve DOX encapsulation efficiencies of 75–85% (percentage of input DOX incorporated) at physiological pH, with release triggered to above 60% within 12–48 hours at pH 5.0 under 808 nm irradiation at 1 W/cm² [15]. In 4T1 murine breast tumor models, combined chemo-PTT using MoS₂-HA-DOX nanosheets

Online ISSN

3007-3197

Print ISSN

3007-3189

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produced tumor volume inhibition rates exceeding 87% over 14 days, compared with approximately 52% for free DOX alone, demonstrating the clear synergy of combining stimulus-responsive drug release with local hyperthermia. The photothermal conversion efficiency of MoS₂ nanosheets typically falls in the range of 24–29% under 808 nm irradiation, which is moderate compared with MXenes or antimonene but sufficient for in vivo tumor ablation when combined with systemic chemotherapy [15]. The photothermal temperature rise (ΔT) achievable in tumor tissue with intravenous MoS₂ platforms is typically reported as 18–25 °C above physiological baseline at doses of 10–20 mg/kg and laser power densities of 0.8–1.5 W/cm². Adding this ΔT to a 37 °C baseline yields final tumor temperatures of approximately 55–62 °C. This temperature range falls within the thermal ablation regime (>50 °C), where irreversible coagulation necrosis occurs within minutes. It should be distinguished from the mild-hyperthermia regime (42–45 °C sustained exposure), which is used for combination therapy with chemotherapy or immunotherapy and requires substantially lower irradiance or shorter duty cycles [19, 10].

MoS₂ platforms have also been explored for cisplatin delivery in cisplatin-resistant ovarian cancer models. Surface-modified MoS₂ nanosheets loaded with cisplatin prodrugs and co-decorated with folic acid targeting ligands achieved IC₅₀ reductions of approximately 3.2-fold relative to free cisplatin in SKOV3 cells, attributed to improved cellular internalization via receptor-mediated endocytosis and bypassing of drug efflux pump-mediated resistance through direct intracellular cargo release following endosomal acidification. These results suggest MoS₂ drug carriers may be particularly valuable in the context of chemotherapy-resistant tumors, an area of urgent clinical unmet need; related receptor-targeted theranostic designs such as mannose-engineered MnO₂-BSA-Au/ICG nanoplatforms illustrate the broader trend toward ligand-directed combination cancer therapy [20].

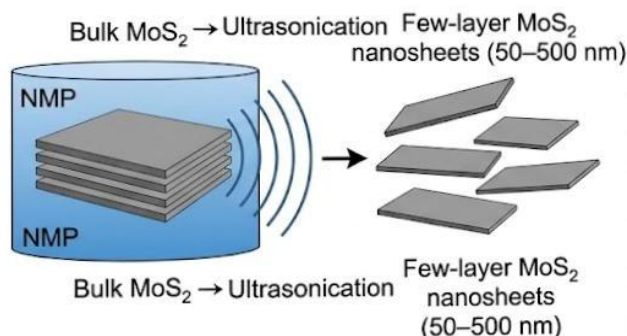


Figure 2. Liquid-phase exfoliation (LPE) of bulk MoS₂ crystals in N-methyl-2-pyrrolidone (NMP) via ultrasonication yields few-layer nanosheets with lateral dimensions of 50–500 nm.

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3007-3197

Print ISSN

3007-3189

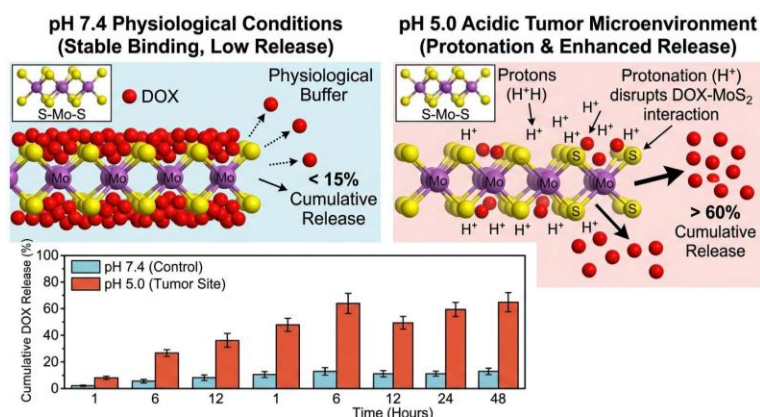
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Figure 3. Consolidated view of pH- and NIR-responsive DOX release from MoS₂ nanosheets. (A) Under physiological conditions (pH 7.4), strong electrostatic interactions stabilize DOX binding to the S–Mo–S surface, resulting in minimal drug release (<15% cumulative release at 48 h). Under the acidic tumor microenvironment (pH 5.0), proton-mediated disruption of DOX–MoS₂ electrostatic interactions triggers enhanced and sustained drug release, exceeding 60% cumulative release within 12 h and approaching 80% by 48 h. (B) NIR irradiation at 808 nm (1 W/cm²) generates a photothermal temperature rise of $\Delta T = 18\text{--}25\text{ }^{\circ}\text{C}$ (final tumor temperature 55–62 $^{\circ}\text{C}$), thermally disrupting drug–nanosheet interactions and accelerating DOX release. (C) Time-dependent cumulative DOX release profile comparing pH 7.4 (control), pH 5.0 (tumor-mimicking), and pH 5.0 + 808 nm NIR (combined chemo-PTT) conditions over 48 h, confirming pH- and NIR-triggered release kinetics suitable for tumor-selective drug delivery.

2.3 WS₂ and MoSe₂ for Imaging-Guided Photothermal Therapy

WS₂ nanosheets exhibit strong NIR absorption and photothermal conversion efficiency in the range of approximately 35–42% under 808 nm irradiation at 1 W/cm². The high atomic number of tungsten ($Z = 74$) provides strong X-ray attenuation, enabling WS₂ to function as both a photothermal agent and a CT contrast agent. MoSe₂ has also been explored for photothermal therapy, photodynamic therapy, photoacoustic imaging, and drug delivery [21]. The dual imaging-therapeutic functionality of WS₂ has been demonstrated in CT-guided photothermal ablation studies. PEGylated WS₂ nanosheets at a dose of 20 mg/kg produced CT signal intensities of 132 HU in tumor tissue, comparable to commercial iodinated contrast agents, while simultaneously achieving tumor surface temperatures above 50 $^{\circ}\text{C}$ under 808 nm irradiation [22]. This combination enables precise delineation of tumor boundaries by CT before and during laser treatment, addressing a key limitation of non-imaging PTT agents that rely on anatomical estimation for laser targeting. In HeLa xenograft mouse models, CT-guided WS₂ PTT produced complete tumor regression in 5 of 8 treated animals over 21 days with no recurrence, compared with partial regression only in mice receiving either CT contrast or laser treatment alone [22, 21].

Online ISSN

3007-3197

Print ISSN

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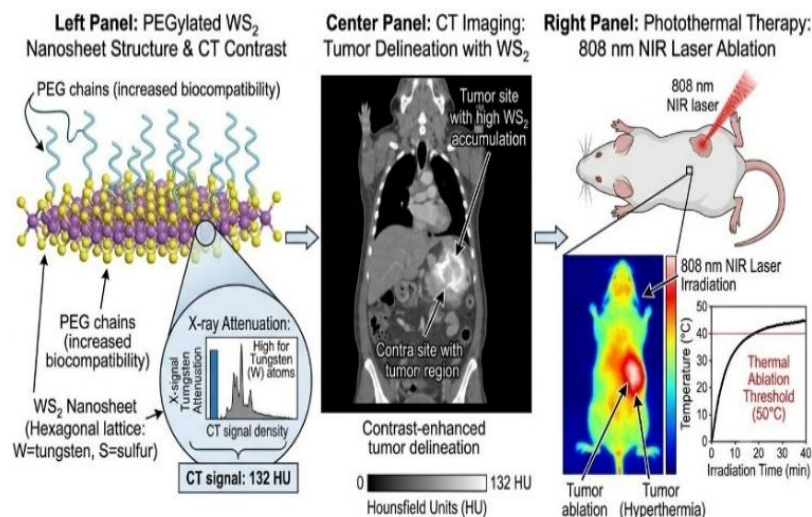
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Figure 4. PEGylated WS₂ nanosheets as a dual CT contrast and photothermal theranostic agent. (A) PEGylated WS₂ nanosheet structure showing hexagonal tungsten-sulfur lattice with PEG chain functionalization for enhanced biocompatibility. The high atomic number of tungsten provides strong X-ray attenuation producing CT signal intensity of 132 Hounsfield Units (HU) in tumor tissue. (B) Contrast-enhanced CT imaging enabling precise tumor delineation with WS₂ accumulation at tumor site compared to contra-lateral control region. (C) NIR photothermal tumor ablation under 808 nm laser irradiation showing thermal imaging of tumor hyperthermia exceeding the 50 °C thermal ablation threshold, with time-temperature curve confirming rapid and sustained heating sufficient for irreversible tumor coagulation necrosis.

WS₂ quantum dots (QDs) represent an important subclass with enhanced photoluminescence for fluorescence bioimaging. Hydrothermal synthesis produces WS₂ QDs with lateral dimensions of 2–5 nm and strong emission at 420–490 nm, enabling blue-channel fluorescence imaging with low cytotoxicity at concentrations up to 200 µg/mL in HeLa, MCF-7, and HepG2 cell lines [22]. The combination of WS₂ QD fluorescence imaging and photothermal ablation in a single nanoplatform illustrates the trend toward theranostic convergence in which a single material performs diagnosis and therapy simultaneously.

MoSe₂ nanosheets possess a bandgap of approximately 1.1 eV in bulk and 1.55–1.66 eV at the monolayer limit, with strong NIR-I window absorption (700–900 nm) making them suitable for photothermal therapy and photoacoustic imaging. The monolayer bandgap of 1.55–1.66 eV corresponds to 750–800 nm (NIR-I), not NIR-II (>1000 nm). In photoacoustic imaging studies, MoSe₂ nanosheets achieved a tumor-delineation detection limit of approximately 8.3–10.2 nM under 808 nm excitation, with photoacoustic signal intensities correlating linearly with nanosheet concentration across a 10–100 µg/mL range [21]. MoSe₂-based photoactivation under NIR irradiation primarily generates ROS via Type I radical pathways (superoxide, hydroxyl radicals) rather than classical Type II singlet oxygen (¹O₂) generation; reported ¹O₂ contributions (quantum yield 0.12–0.18) likely reflect minor Type II activity or visible-wavelength excitation contributions. The dominant therapeutic mechanism at 808 nm is photothermal, with ROS serving as a secondary stress pathway sufficient for

combination PTT + oxidative therapy protocols [21, 19].

2.4 Multimodal TMD Theranostic Platforms

A major trend in TMD biomedical research is the design of multifunctional theranostic nanoplatforms that integrate diagnosis and therapy. Representative examples include MoS₂/Fe₃O₄ hybrids for MRI-guided photothermal therapy, WS₂ quantum dots for fluorescence imaging and photothermal therapy, MoSe₂ nanosheets for photoacoustic imaging and multimodal therapy, MoS₂-based siRNA vectors for combined gene silencing and photothermal therapy, and Gd-doped TMDs for MRI enhancement [19, 23]. The unifying principle is that a single TMD nanosheet can simultaneously carry imaging contrast (X-ray, MRI, fluorescence, or photoacoustic), therapeutic cargo (drug, gene, or photothermal), and targeting ligands, reducing the cumulative injection burden on the patient and enabling image-guided treatment that confirms successful tumor accumulation before therapeutic activation.

2.5 Gene Delivery and Immunotherapy with TMDs

TMD nanosheets can interact with nucleic acids through electrostatic and van der Waals interactions, enabling delivery of siRNA, miRNA, and plasmid DNA targeting oncogenes or resistance pathways. MoS₂ nanosheets modified with polyethylenimine (PEI) or branched cationic polymers form stable complexes with siRNA at N/P ratios above 5, with zeta potentials of +15 to +25 mV facilitating efficient cellular uptake [19, 24]. In multidrug-resistant MCF-7/ADR breast cancer models, MoS₂-PEI-siRNA complexes targeting the P-glycoprotein efflux gene achieved 78% mRNA knockdown efficiency, reducing the IC₅₀ of co-delivered doxorubicin by approximately fivefold and producing 94% tumor inhibition in xenograft models over 21 days [24].

Combined with photothermal therapy, gene delivery can suppress survival pathways in residual cancer cells. TMD-based photothermal therapy may also induce immunogenic cell death (ICD), promoting dendritic cell maturation and potentially synergizing with immune checkpoint inhibitors [19, 25]. MoS₂-mediated PTT has been shown to release calreticulin, HMGB1, and ATP as damage-associated molecular patterns (DAMPs) from dying tumor cells, activating the innate immune cascade and priming cytotoxic T lymphocyte responses. When combined with anti-PD-1 checkpoint blockade in bilateral CT26 colon tumor models, MoS₂ PTT-induced ICD suppressed not only irradiated primary tumors but also produced significant inhibition of non-irradiated distant tumors through systemic immune activation, with distant tumor inhibition rates of approximately 65% versus 12% in checkpoint blockade alone groups [19, 23]. These findings position TMD-mediated PTT as an in situ cancer vaccination strategy capable of converting a local treatment into systemic antitumor immunity, a concept of growing importance in immuno-oncology and complementary to biomineralization-inspired autologous cancer vaccine approaches [25, 26]. Collectively, TMD-based gene delivery and immunotherapy platforms represent a convergence of precision medicine principles with nanomaterial engineering, positioning them as strong candidates for next-generation combination cancer therapy.

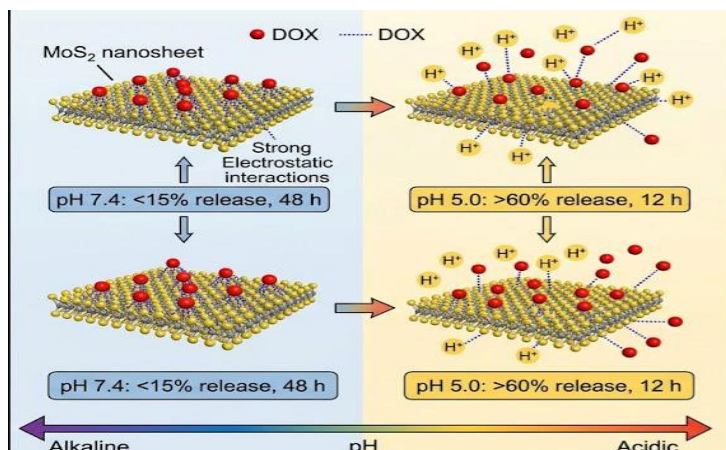


Figure 5. pH-responsive DOX release from MoS₂ nanosheets. At physiological pH 7.4, strong electrostatic interactions retain DOX on the S–Mo–S surface (<15% release, 48 h). Under acidic tumor microenvironment conditions (pH 5.0), protonation disrupts DOX–MoS₂ binding, triggering >60% cumulative release within 12 h.

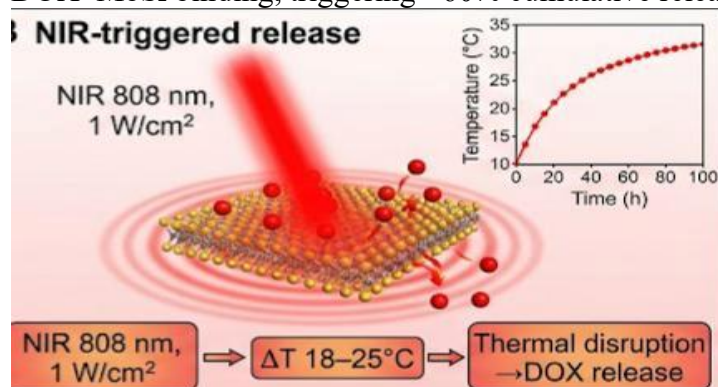


Figure 6. NIR-triggered DOX release from MoS₂ nanosheets. Irradiation at 808 nm (1 W/cm²) generates a photothermal temperature rise of $\Delta T = 18\text{--}25^\circ\text{C}$, thermally disrupting drug–nanosheet interactions and accelerating DOX release

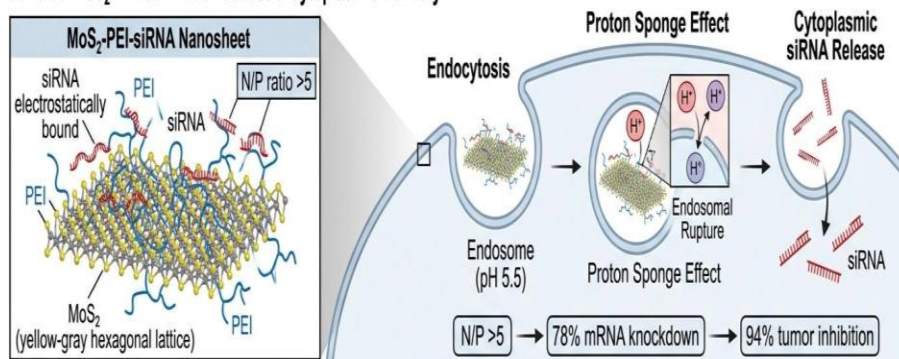


Figure 7. MoS₂-PEI-siRNA nanosheet construction and cytoplasmic siRNA delivery mechanism. PEI-functionalized MoS₂ nanosheets electrostatically complex siRNA at N/P ratio >5, enabling endocytosis-mediated cellular uptake. Endosomal acidification (pH 5.5) triggers the proton-sponge effect causing endosomal rupture and cytoplasmic siRNA release, achieving 78% mRNA knockdown and 94% tumor inhibition in

Online ISSN

3007-3197

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3007-3189

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xenograft models.

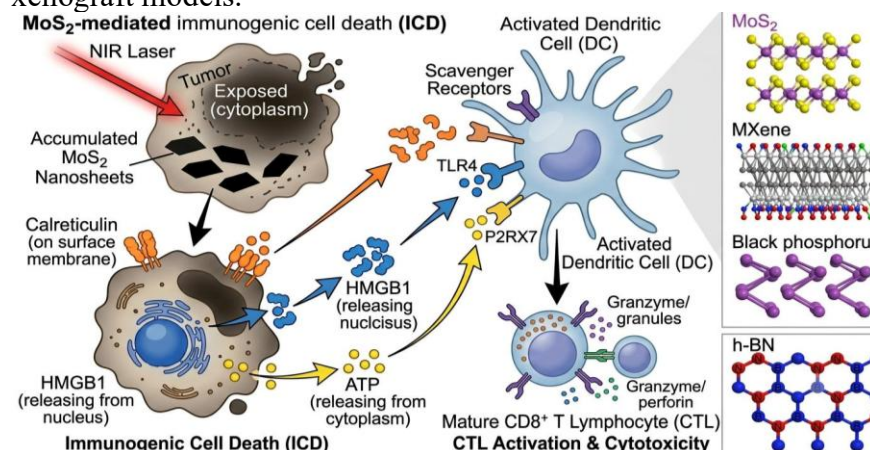


Figure 8. Mechanism of MoS₂-mediated immunogenic cell death (ICD) and downstream antitumor immune activation. Near-infrared (NIR) laser irradiation of MoS₂-accumulated tumor cells induces photothermal damage, triggering release of damage-associated molecular patterns (DAMPs), surface-exposed calreticulin, nuclear HMGB1, and cytoplasmic ATP. These DAMPs engage their respective receptors (scavenger receptors, TLR4, and P2RX7) on dendritic cells (DCs), driving DC maturation and antigen presentation. Activated DCs subsequently prime CD8⁺ cytotoxic T lymphocytes (CTLs), which mediate granzyme/perforin-dependent tumor cell killing. Inset panels show the crystal structures of representative 2D nanomaterials (MoS₂, MXene, black phosphorus, and h-BN) capable of inducing comparable ICD responses.

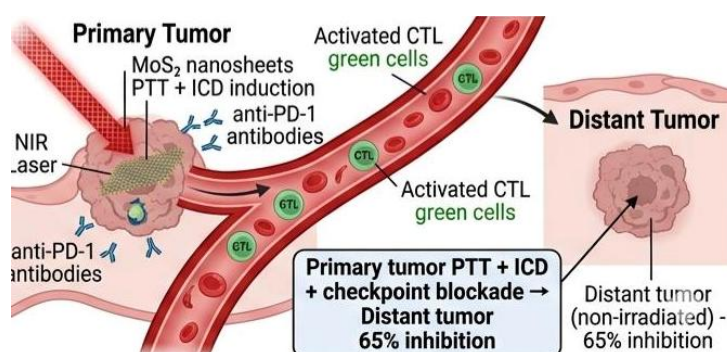


Figure 9. Systemic abscopal effect through combined MoS₂ PTT, ICD induction, and anti-PD-1 checkpoint blockade. Activated CTLs travel through vasculature from primary irradiated tumor to suppress non-irradiated distant tumors, achieving ~65% distant tumor inhibition in bilateral preclinical models, converting local photothermal treatment into systemic antitumor immunity.

Table 1. Chemical Formulas, Crystal Structures, and Unit Cell Parameters of Key 2D Materials

Material	Chemical Formula	Crystal Structure	Unit Cell / Key Parameters	Phase
MoS ₂ (2H phase)	MoS ₂	Trigonal prismatic (2H); P6 ₃ /mmc	a = 3.16 Å; bandgap 1.2 eV (bulk) → 1.8–1.9 eV (monolayer, direct)	2H semiconductor
WS ₂ (2H phase)	WS ₂	Trigonal prismatic (2H); P6 ₃ /mmc	a = 3.15 Å; bandgap 1.4–1.98 eV; PCE 35–42% at 808 nm	2H semiconductor
Ti ₃ C ₂ T _x MXene	Ti ₃ C ₂ T _x	Hexagonal layered (P6 ₃ /mmc); delaminated multilayer	a = 3.07 Å; conductivity 2,000–20,000 S/cm; surface area 200.8 m ² /g	Delaminated 2D carbide
Nb ₂ CT _x MXene	Nb ₂ CT _x	Hexagonal layered; from Nb ₂ AlC MAX phase	PCE 36.4% at 808 nm; biodegradable MXene candidate	2D carbide; biodegradable
Black phosphorus	P	Puckered orthorhombic; Cmce	E _g 0.3 eV (bulk) → ~2.0 eV (monolayer phosphorene, direct)	Orthorhombic semiconductor
h-BN	BN (hexagonal)	Graphite-like; P6 ₃ /mmc	a = 2.50 Å; bandgap 6.0 eV; thermal conductivity 400 W/m/K (bulk in-plane)	Wide-bandgap insulator
Antimonene (β)	Sb	Buckled hexagonal; P-3m1 (No. 156)	a = 4.12 Å; PCE 45.5% (PEGylated QDs) at 808 nm, 1 W/cm ²	β-antimonene; semiconductor
Borophene (χ ³)	B	χ ³ phase on Ag(111); hollow hexagonal; metallic	AFM thickness ~1.10 nm; Raman: 296, 452, 783 cm ⁻¹	χ ³ crystalline; metallic

Abbreviations: TMD = transition metal dichalcogenide; LPE = liquid-phase exfoliation; PCE = photothermal conversion efficiency. PCE values were determined by the time-constant method (Roper et al. 2007) unless otherwise noted and should be interpreted as order-of-magnitude indicators rather than as precise inter-material

rankings.

Table 2. Representative TMD Theranostic Nanoplatfroms

Material	Functionalization	Cargo Function /	Therapy Mode	Imaging Mode	Key Outcome
MoS ₂	PEG	Doxorubicin	Chemo + PTT	Photoacoustic	pH/NIR-responsive release and tumor inhibition
WS ₂	PEG	Photothermal agent	PTT	CT / PA	CT-guided tumor ablation
MoSe ₂	Polymer / drug	DOX / photosensitizer	PTT + PDT + chemo	PA	Multimodal cancer theranostics
MoS ₂ /Fe ₃ O ₄	Magnetic hybrid	Drug carrier	PTT + chemo	MRI	MRI-guided treatment
MoS ₂ -siRNA	PEI / polymer	siRNA	Gene therapy + PTT	—	Gene knockdown and thermal killing

3. MXenes in Biomedicine: Photothermal Therapy, Antibacterial Activity, Immunotherapy and Neural Interfaces

3.1 Structure, Synthesis and Surface Chemistry

MXenes are two-dimensional transition metal carbides, nitrides, and carbonitrides with the general formula $M_{n+1}X_nT_x$, where M is an early transition metal, X is carbon or nitrogen, and T_x represents surface terminations such as $-OH$, $=O$, $-F$, and $-Cl$. $Ti_3C_2T_x$ is the most studied MXene in biomedical applications [27, 28]. MXenes are synthesized by selectively etching the A-layer from MAX phase precursors such as Ti_3AlC_2 [8, 29, 30]. The selective-extraction concept has been reviewed extensively by Naguib and Gogotsi [30], and the broader family of MXenes as a new class of 2D materials was introduced in 2014 [31]. Milder LiF/HCl methods and electrochemical etching are increasingly preferred over traditional concentrated HF etching because they reduce hazardous handling and produce MXenes with lower residual fluoride contamination, improving colloidal stability and reducing potential fluoride-associated cytotoxicity, while achieving broadly similar surface termination chemistry ($-F$, $-OH$, $=O$). The role of acid-mixture composition on the surface chemistry and ion-storage properties of $Ti_3C_2T_x$ has been systematically characterized [32, 33].

Online ISSN

3007-3197

Print ISSN

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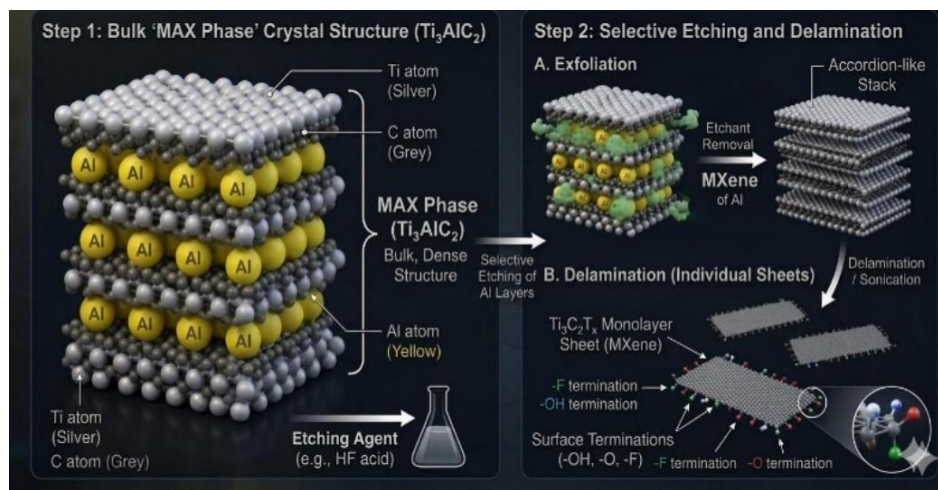
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Figure 10. Schematic illustration of MXene synthesis from MAX phase precursor for biomedical applications. (Step 1) Bulk MAX phase (Ti_3AlC_2) crystal structure consisting of Ti (silver), Al (yellow), and C (grey) atomic layers arranged in a dense, layered configuration. (Step 2) Selective chemical etching of the Al layers using an etching agent (e.g., HF or LiF/HCl), yielding an "accordion-like" multilayered structure with expanded interlayer spacing. (Step 3) Delamination via sonication or mechanical agitation produces individual $\text{Ti}_3\text{C}_2\text{T}_x$ MXene monolayers. The surface is terminated with hydrophilic functional groups ($-\text{OH}$, $-\text{O}$, and $-\text{F}$) that enhance colloidal stability, enable biomolecule conjugation, and facilitate drug loading, photothermal therapy, and biosensing applications.

3.2 MXene Photothermal Cancer Therapy

$\text{Ti}_3\text{C}_2\text{T}_x$ exhibits broad absorption across NIR-I and NIR-II biological windows, with photothermal conversion efficiency reported between approximately 28% and 50% depending on synthesis route, flake thickness, and laser wavelength. Surface coatings such as soybean phospholipid, PEG, polyvinylpyrrolidone (PVP), and albumin improve physiological stability. Non-Ti MXenes are also important: Nb_2CT_x combines strong NIR-I/NIR-II photothermal performance with improved biodegradability, while $\text{Ta}_4\text{C}_3\text{T}_x$, due to the high atomic number of tantalum ($Z = 73$), can provide CT contrast in addition to photothermal therapy; two-dimensional tantalum carbide MXene composite nanosheets have been demonstrated for multiple imaging-guided photothermal tumor ablation [34, 35].

3.3 MXene-Composite Chemo-Photothermal and Catalytic Therapy

MXenes can load chemotherapeutic agents such as doxorubicin through electrostatic and non-covalent interactions, with drug release triggered by acidic pH, glutathione, or NIR irradiation. MXene-composite catalytic therapy has also emerged, in which an iron-oxide-decorated MXene promotes Fenton-like reactions in the tumor microenvironment: the Fe_3O_4 component provides the $\text{Fe}^{2+}/\text{Fe}^{3+}$ catalyst that converts endogenous hydrogen peroxide into cytotoxic hydroxyl radicals, while the MXene provides photothermal heating that accelerates Fenton kinetics. The phrase "MXene-based catalytic therapy" should be interpreted as "MXene-composite-mediated Fenton catalysis", the MXene itself does not directly catalyze the Fenton reaction [36].

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Quantitative performance data for MXene chemo-PTT platforms are instructive. $\text{Ti}_3\text{C}_2\text{T}_x$ nanosheets functionalized with PEG and loaded with DOX achieve loading efficiencies of 70–80% at pH 7.4, releasing over 75% of cargo within 24 hours at pH 5.0 under NIR irradiation at 1 W/cm^2 , compared with only 18% release under physiological conditions [8, 36]. The pH-responsive release is attributed to disruption of electrostatic DOX–MXene interactions in the acidic tumor microenvironment, a mechanism that provides a degree of tumor selectivity important for limiting systemic drug exposure. In 4T1 tumor-bearing BALB/c mice, DOX-loaded PEG- $\text{Ti}_3\text{C}_2\text{T}_x$ nanosheets produced tumor inhibition rates of 92% over 16 days under combined chemo-PTT conditions, with no significant body weight loss or organ histopathological changes observed at therapeutic doses of 10 mg/kg , suggesting acceptable acute systemic tolerability in this model [8, 36].

For catalytic therapy, Fe_3O_4 -decorated $\text{Ti}_3\text{C}_2\text{T}_x$ MXene composites exploit the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^\bullet + \text{OH}^-$) to generate hydroxyl radicals selectively within the H_2O_2 -enriched tumor microenvironment. The NIR-triggered local heating from the MXene component accelerates the Fenton reaction kinetics approximately 3.2-fold at 45°C compared with 37°C (consistent with the Arrhenius-based Q_{10} of approximately 2–3 for Fenton chemistry), creating a synergy between PTT and chemodynamic therapy [36]. This thermally accelerated Fenton-MXene system demonstrated cell viability below 10% in HeLa cells at $100 \mu\text{g/mL}$ under 808 nm irradiation, compared with approximately 40% viability for Fenton catalysis alone and 55% for PTT alone, confirming the combinatorial benefit [36].

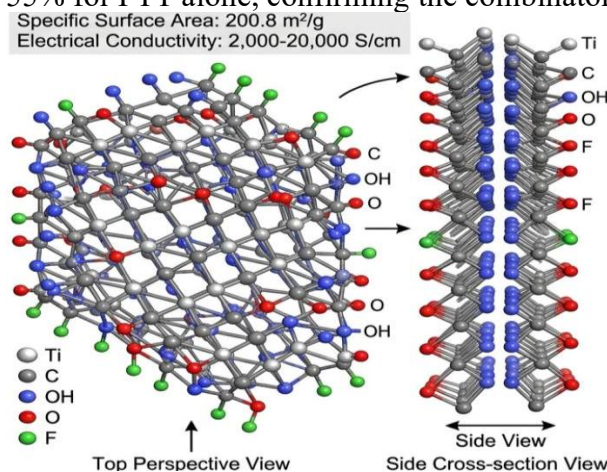


Figure 11. MXene-composite chemo-photothermal and catalytic therapy mechanism. (A) PEGylated $\text{Ti}_3\text{C}_2\text{T}_x$ nanosheet loaded with doxorubicin (DOX) via electrostatic interactions, achieving 70–80% drug loading at pH 7.4. (B) Tumor-microenvironment-responsive drug release: at pH 5.0 + 808 nm NIR irradiation, >75% DOX release within 24 h versus <18% at pH 7.4. (C) Fe_3O_4 -decorated MXene composite promoting Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{HO}^\bullet + \text{OH}^-$), with NIR heating accelerating Fenton kinetics ~ 3.2 -fold at 45°C , yielding <10% HeLa cell viability at $100 \mu\text{g/mL}$ under combined chemo-PTT-catalytic therapy.

3.4 Antibacterial Coatings and Wound Healing

MXenes exhibit antibacterial activity through multiple mechanisms including physical

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3007-3197

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3007-3189

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disruption of bacterial membranes by sharp nanosheet edges, surface-mediated ROS generation, NIR-triggered local heating, and support of wound monitoring via conductive coatings. MXene-incorporated hydrogels and wound dressings have been tested against *Staphylococcus aureus*, MRSA, and *Escherichia coli*, combining antibacterial action, moisture retention, anti-inflammatory drug delivery, and real-time wound monitoring [37, 38].

Quantitative antibacterial performance benchmarks for $\text{Ti}_3\text{C}_2\text{T}_x$ MXene have been established across multiple study designs. $\text{Ti}_3\text{C}_2\text{T}_x$ nanosheets at concentrations of 100 $\mu\text{g/mL}$ produced >99% killing of *S. aureus* and *E. coli* within 4 hours in direct contact assays, with minimum inhibitory concentrations (MICs) of 32–64 $\mu\text{g/mL}$ for *S. aureus* and 16–32 $\mu\text{g/mL}$ for *E. coli* in broth microdilution assays [37]. These MIC values depend strongly on flake size, thickness, and surface termination chemistry, which should be specified when comparing across studies. Critically, MXene nanosheets retained antibacterial activity against methicillin-resistant *S. aureus* (MRSA), for which antibiotic options are severely limited, with 95% colony-forming unit reduction at 128 $\mu\text{g/mL}$ [38]. The sharp edge-mediated membrane disruption mechanism was confirmed by scanning electron microscopy showing bacterial cell envelope damage and scanning transmission electron microscopy revealing MXene nanosheet internalization within disrupted bacterial cells, distinguishing this physical killing mode from conventional antibiotic mechanisms that are susceptible to resistance development [37].

MXene-composite wound dressings represent the most clinically relevant application of this antibacterial activity. $\text{Ti}_3\text{C}_2\text{T}_x$ -incorporated polyvinyl alcohol (PVA) hydrogel dressings with embedded silver nanoparticles demonstrated synergistic antibacterial zones of inhibition (ZOI) of 22 mm against MRSA versus 14 mm for AgNP-only dressings and 9 mm for $\text{Ti}_3\text{C}_2\text{T}_x$ -only dressings, confirming the antibacterial synergy [38]. In full-thickness wound healing models in diabetic rats, $\text{Ti}_3\text{C}_2\text{T}_x/\text{PVA}/\text{AgNP}$ composite dressings achieved $97.3 \pm 1.2\%$ wound closure by day 14 compared with $72.4 \pm 3.6\%$ for standard gauze dressings and $85.1 \pm 2.8\%$ for AgNP-only dressings, attributed to combined antibacterial protection, moist wound environment maintenance, and mild photothermal stimulation promoting angiogenesis and collagen deposition [38, 39].

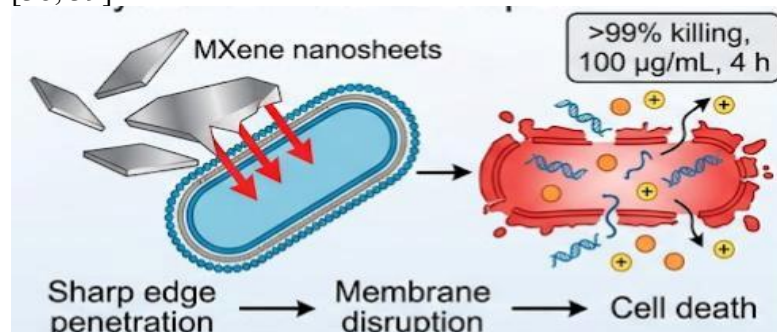


Figure 12. MXene-composite wound dressing for antibacterial and photothermal wound healing. (A) $\text{Ti}_3\text{C}_2\text{T}_x/\text{PVA}/\text{AgNP}$ hydrogel dressing structure combining MXene nanosheets (sharp-edge membrane disruption), silver nanoparticles (Ag^+ release), and PVA matrix (moist environment retention). (B) Antibacterial zones of inhibition against MRSA: 22 mm (composite) vs. 14 mm (AgNP-only) vs. 9 mm

(MXene-only). (C) Full-thickness wound healing in diabetic rat model: $97.3 \pm 1.2\%$ wound closure at day 14 for composite dressing vs. $72.4 \pm 3.6\%$ for gauze control, attributed to combined antibacterial, photothermal, and angiogenic effects.

3.5 MXene Immunotherapy

MXene-mediated tumor hyperthermia induces calreticulin exposure, ATP secretion, HMGB1 release, and dendritic cell activation. Combined with immune checkpoint blockade such as anti-PD-L1 therapy, MXene PTT can convert local tumor ablation into systemic antitumor immunity. In bilateral tumor models, irradiation of one tumor combined with checkpoint blockade has produced suppression of nonirradiated distant tumors, demonstrating an abscopal effect [8]. This immunotherapeutic synergy parallels the ICD cascade described for MoS₂ PTT (Section 2.5), suggesting that any 2D material capable of inducing controlled tumor-cell necrosis with concomitant DAMP release can be harnessed as an in situ vaccination adjuvant. The clinical implication is that 2D-material-mediated PTT may find its strongest translational niche not as a standalone tumor-ablation technique but as a component of combination immunotherapy regimens, particularly for tumors poorly responsive to checkpoint blockade alone.

3.6 MXene Neural Interfaces

Neural interfaces require materials combining high conductivity, low impedance, biocompatibility, mechanical flexibility, and chronic stability. Ti₃C₂T_x-coated flexible electrodes show low impedance, high charge storage capacity, and improved signal-to-noise ratio compared with conventional metal electrodes [40, 41]. Key advantages include low impedance at neural recording frequencies, high charge injection capacity for stimulation, flexible processing on Parylene-C, polyimide, and elastomeric substrates, and strong performance in electrocorticography (ECoG), local field potential, and single-unit recordings.

Quantitative electrophysiological characterization demonstrates that Ti₃C₂T_x-coated Parylene-C electrodes achieve impedances of 5–30 k Ω at 1 kHz, approximately a 20–100-fold reduction versus bare Pt/Ir electrodes of matched geometric area (typically 200–500 k Ω for 50–100 μ m diameter sites), directly improving signal-to-noise ratio for single-unit detection [40, 41]. Charge injection capacities of 1–5 mC/cm² (with values up to approximately 10 mC/cm² reported under expanded voltage windows) enable safer electrical stimulation at lower voltages, reducing the risk of faradaic tissue damage [40]. The upper bound of ~ 10 mC/cm² should be qualified by the specific pulse protocol and voltage window; values in the 1–5 mC/cm² range are more typical for chronic stimulation paradigms.

In chronic 8-week rodent implantation studies, MXene ECoG arrays maintained recording quality with less than 30% impedance increase and single-unit yields above 70% of baseline, compared with 50–80% yield degradation for conventional metal Utah arrays, attributed to the substantially reduced mechanical mismatch between MXene-polymer composites (effective modulus 2.5 GPa) and brain tissue (0.1–1 kPa) versus silicon-based Utah arrays (130 GPa) which is approximately a 50-fold reduction in modulus. Note that all current electrode materials remain orders of magnitude stiffer than brain tissue (0.1–1 kPa), and the ~ 2.5 GPa value represents a relative, not absolute, improvement in compliance [40, 42, 41]. The chronic stability advantage of MXene

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3007-3197

Print ISSN

3007-3189

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arrays has direct implications for brain-computer interface (BCI) applications, where sustained single-unit recording quality over months to years determines whether the implant remains clinically useful for prosthetic control, communication, or seizure detection in patients with severe motor disabilities.

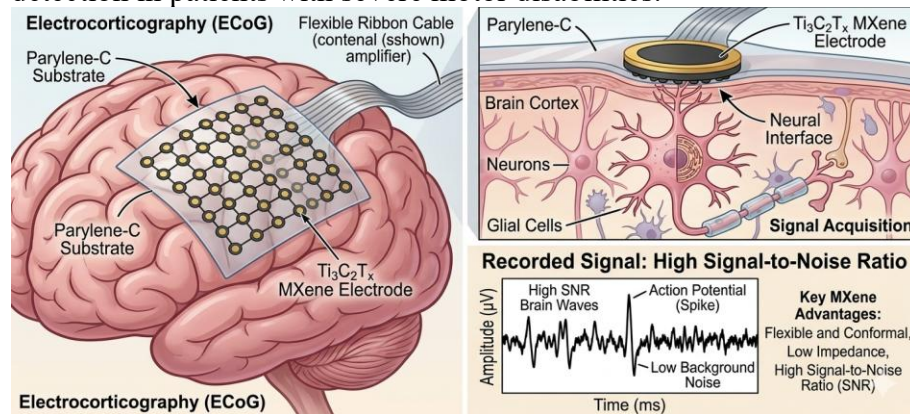


Figure 13. Ti₃C₂T_x MXene electrocorticography (ECoG) array for cortical neural recording and signal acquisition. (A) Flexible Parylene-C substrate supporting a 16–64 channel grid of Ti₃C₂T_x electrodes (50–100 μm diameter) conformally placed on the brain cortex surface for high-density neural recording. (B) Electrode-tissue interface showing Ti₃C₂T_x MXene electrode in direct contact with neurons and glial cells, achieving low impedance (5–30 kΩ at 1 kHz), high charge injection capacity (>1 mC/cm²), and high SNR enabling simultaneous local field potential (LFP, 0.5–100 Hz) and single-unit spike detection (300 Hz–5 kHz) with minimal background noise.

Table 3. Neural Electrode Material Comparison

Electrode Material	Impedance at 1 kHz	Signal-to-Noise Ratio	Charge Injection Capacity	Key Advantage
Bare Pt/Ir	~200 kΩ – 1 MΩ	Moderate (established clinical standard)	~0.05–0.15 mC/cm ²	Clinical track record; established safety
PEDOT:PSS	~10–100 kΩ	Moderate–High	~1–5 mC/cm ²	Mixed ionic-electronic conduction; soft mechanics
Graphene	~50–200 kΩ	High	~0.5–3 mC/cm ²	Optical transparency; broadband DC–THz recording

Electrode Material	Impedance at 1 kHz	Signal-to-Noise Ratio	Charge Injection Capacity	Key Advantage
Ti ₃ C ₂ T _x MXene	~5–30 kΩ	High; superior to Pt/Ir	>1 mC/cm ² (up to ~10 mC/cm ²)	Metallic conductivity; flexible substrate compatibility

4. Black Phosphorus: Biodegradable Theranostics and Tissue Engineering

4.1 Structure and Key Properties

Black phosphorus is a layered allotrope of phosphorus with a puckered orthorhombic crystal structure (space group Cmce). Its bandgap is direct and thickness-dependent, ranging from approximately 0.3 eV in bulk to about 2.0 eV in monolayer phosphorene, enabling strong optical absorption across visible and near-infrared wavelengths. Ultrasmall black phosphorus quantum dots synthesized via solvent-exfoliation routes have extended the photothermal-agent toolbox into the sub-5 nm regime [43]. Unlike many inorganic 2D materials, BP degrades under aqueous and oxidative conditions into phosphate species specifically, at physiological pH 7.4, the dominant species are HPO₄²⁻ (61%) and H₂PO₄⁻ (39%), reflecting the second (pK_{a2} = 7.21) and first (pK_{a1} = 2.16) dissociation equilibria of phosphoric acid. The fully deprotonated PO₄³⁻ form (pK_{a3} = 12.35) is negligible below pH 10 and is not a direct BP degradation product at physiological pH. These phosphate species are naturally involved in biological phosphate metabolism and bone mineralization [44, 45]. Structurally related group-V monoelemental analogues, such as tin sulfide nanosheets, have been explored as alternative NIR photothermal agents with comparable layered-honeycomb motifs [46].

4.2 Biodegradability as a Biomedical Advantage

The biodegradability of BP is one of its most important biomedical advantages, offering a potential self-eliminating alternative to materials that accumulate in organs. However, rapid oxidation can reduce shelf life and shorten therapeutic windows, necessitating surface stabilization strategies including PEGylation, polydopamine coating, chitosan encapsulation, PLGA incorporation, and Al₂O₃ or TiO₂ passivation [47]. The trade-off between biodegradation rate and functional stability must be carefully tuned for each application: cancer theranostics favors rapid degradation after tumor treatment to minimize residual accumulation, while bone tissue engineering requires sustained BP presence over weeks to support osteogenic differentiation and mineralization. This tuning is typically achieved by adjusting PEG chain length, polymer encapsulation thickness, or inorganic passivation layer density.

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3007-3197

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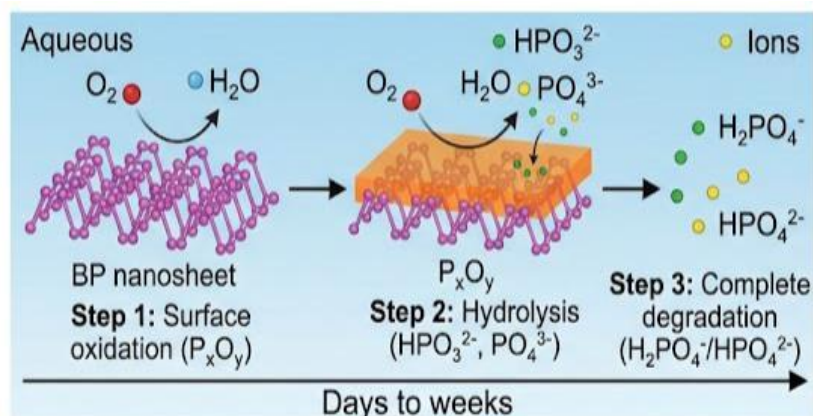
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Figure 14. Biodegradation pathway of black phosphorus (BP) into biocompatible phosphate species. BP nanosheets undergo oxidative degradation in aqueous and biological media, producing HPO_4^{2-} (61%) and $H_2PO_4^-$ (39%) at physiological pH 7.4, reflecting the second ($pK_{a2} = 7.21$) and first ($pK_{a1} = 2.16$) dissociation equilibria of phosphoric acid. These phosphate species enter the normal phosphate metabolic pool and are excreted renally or incorporated into bone mineral. The fully deprotonated PO_4^{3-} form ($pK_{a3} = 12.35$) is negligible below pH 10 and is not a direct BP degradation product at physiological pH.

4.3 BP for Cancer Theranostics

BP nanosheets and quantum dots can perform photothermal therapy under NIR irradiation and generate reactive oxygen species for photodynamic and sonodynamic therapy. Biodegradable BP-based nanospheres were among the earliest formulations demonstrated for in vivo photothermal cancer therapy [48, 43]. Smart NIR-light-controlled drug-release nanostructures based on BP have provided additional stimulus-responsive cargo-release modalities [49]. Combined BP-based therapy often integrates PTT, PDT, sonodynamic therapy (SDT), chemotherapy with pH-responsive drug release, and bioimaging into multimodal platforms that have produced strong tumor inhibition in preclinical models, with BP achieving up to 50 wt% DOX loading which is amongst the highest of any 2D material [44, 9]. BP-based multimodal nanoagents have also been engineered to address tumor hypoxia, a common resistance mechanism that limits the efficacy of single-modality PTT and PDT [50].

Specific performance benchmarks for BP-based cancer theranostics are well established. PEGylated BP nanosheets achieve photothermal conversion efficiencies of 28–36% under 808 nm irradiation, with tumor temperatures rising to 50–55 °C within 10 minutes at doses of 5 mg/kg and laser power densities of 1 W/cm² in subcutaneous tumor models [44]. These temperatures exceed the threshold for thermal coagulation necrosis (>50 °C) and are sufficient for tumor ablation. The mild-hyperthermia regime of 42–45 °C applies to lower-irradiance combination therapy regimens, not to the ablation regimens described here. DOX-loaded BP nanosheets exhibited pH-responsive release profiles with less than 15% cumulative DOX release at pH 7.4 over 48 hours but greater than 80% release at pH 5.0, providing selectivity for the acidic tumor microenvironment [44, 9]. In 4T1 xenograft models, BP-PEG-DOX combined chemo-PTT produced 91% tumor inhibition over 18 days, with no detectable tumor metastasis

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3007-3197

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3007-3189

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to lung by histology, compared with 68% inhibition for PTT alone and 45% for chemotherapy alone at equivalent doses [44].

The sonodynamic therapy (SDT) capability of BP is particularly notable because it enables treatment of deep-seated tumors inaccessible to NIR-I light (700–900 nm), which has a tissue penetration depth limited to approximately 1–2 cm. NIR-II light at 1000–1700 nm penetrates 3–5 cm but requires appropriate photoabsorbers. Ultrasound is not limited by optical tissue penetration and can reach any depth in soft tissue. BP quantum dots under ultrasound irradiation (1 MHz, 1 W/cm²) generated ¹O₂ and superoxide radicals sufficient to induce apoptosis in over 70% of HeLa cells in vitro at 50 µg/mL, with in vivo deep-tissue SDT in subcutaneous tumor models showing 78% tumor growth inhibition at tumor depths of 2–3 cm inaccessible to laser-driven PTT [9]. This ultrasound activation pathway substantially broadens the clinical applicability of BP beyond surface or minimally invasive tumors.

4.4 BP for Bone Tissue Engineering

BP is especially attractive for bone regeneration because phosphate release promotes hydroxyapatite formation and osteogenic differentiation. When incorporated into PLGA, PLA, bioactive glass, or hydrogel scaffolds, BP supports mineralization, promotes osteogenic markers such as alkaline phosphatase and RUNX2, provides mild photothermal stimulation to enhance osteoblast differentiation, and improves angiogenesis [47, 51]. Exfoliated BP has been demonstrated to promote in vitro bone regeneration and to support angiogenesis, and BP hydrogel scaffolds have been shown to enhance bone regeneration via a sustained supply of calcium-free phosphorus [52, 53]. 2D-BP-reinforced 3D-printed scaffolds have additionally been investigated as a stepwise countermeasure against osteosarcoma, combining tumor ablation with bone regeneration in a single platform [54].

Quantitative data from bone tissue engineering studies reinforce the unique advantages of BP as a bioactive scaffold component. BP-PLGA composite scaffolds at BP loading levels of 0.5–2 wt% achieved calcium deposition values of 3.8–4.9-fold above unseeded scaffold controls and 1.8–2.4-fold above PLGA-only controls after 21 days of osteoblast culture, with alkaline phosphatase (ALP) activity at 14 days reaching 3.1 U/mg protein compared with 1.2 U/mg for PLGA controls [55]. RUNX2 and osteocalcin gene expression in hMSCs cultured on BP scaffolds were upregulated 4.2–5.8-fold and 3.1–4.4-fold respectively compared with tissue culture plastic, confirming osteogenic commitment [55, 56].

The phosphate degradation products of BP (HPO₄²⁻ and H₂PO₄⁻ at physiological pH) contribute to hydroxyapatite (HA, Ca₁₀(PO₄)₆(OH)₂) nucleation in the presence of calcium ions. HA requires PO₄³⁻ ions in its crystal structure, but PO₄³⁻ is not the direct BP degradation product at pH 7.4. Instead, HPO₄²⁻ is locally deprotonated to PO₄³⁻ at the Ca²⁺-rich, mildly alkaline nucleation microenvironment at the mineralization site, enabling HA crystallite formation. X-ray diffraction confirms HA crystallite formation on BP-containing scaffolds by day 14, significantly earlier than on control scaffolds [55]. BP degradation products also promote osteogenesis via phosphate-signaling pathways independent of HA mineralization [52].

In critical-size calvarial defect models in rats, BP-incorporated bioactive glass scaffolds produced 89 ± 4% bone area fill by week 8 compared with 52 ± 7% for plain bioactive

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glass and $31 \pm 5\%$ for untreated defects, with histological evidence of organized lamellar bone formation and vascular ingrowth [47]. Mild photothermal stimulation ($40\text{--}42^\circ\text{C}$, sub-ablative) of BP scaffolds via transcutaneous 808 nm irradiation further enhanced vascularization, with CD31-positive vessel density 2.3-fold higher in thermally stimulated BP scaffold groups versus non-irradiated BP scaffold controls, consistent with evidence that mild hyperthermia promotes VEGF secretion and endothelial migration [47].

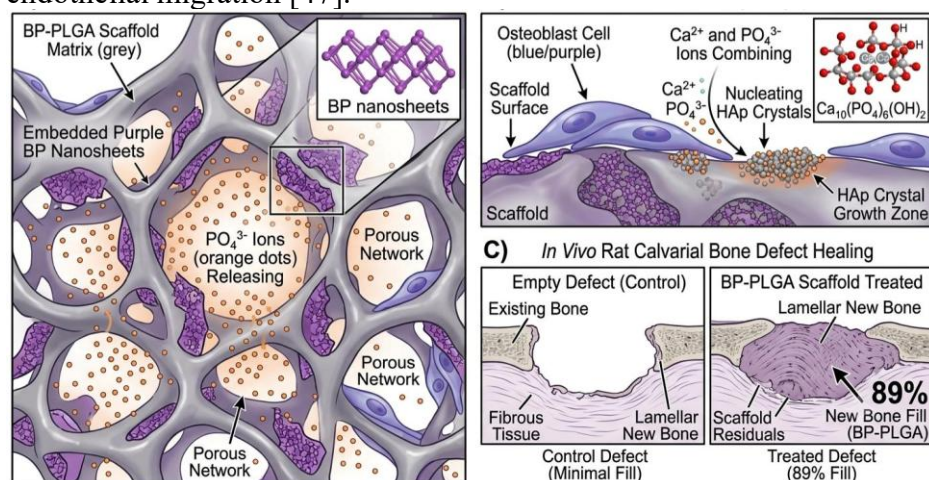


Figure 15. BP-PLGA/bioactive glass composite scaffold for bone tissue regeneration and defect healing. (A) Porous scaffold structure showing BP nanosheets embedded within PLGA/bioactive glass 3D mesh, with BP degradation releasing phosphate species ($\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ at physiological pH) into scaffold pores. (B) Hydroxyapatite (HA) nucleation and osteoblast attachment: the HPO_4^{2-} released by BP degradation is locally deprotonated to PO_4^{3-} at the Ca^{2+} -rich nucleation microenvironment, providing the PO_4^{3-} substrate for HA crystal nucleation. BP-PLGA scaffolds achieve 3.8–4.9-fold higher calcium deposition, alkaline phosphatase (ALP) activity of 3.1 U/mg, and RUNX2 upregulation of 4.2–5.8-fold compared to controls. (C) In vivo calvarial bone defect healing showing $89 \pm 4\%$ bone area fill at week 8 with organized lamellar bone formation compared to empty defect control.

4.5 BP for Wound Healing and Transient Implants

BP-based hydrogels and wound dressings can accelerate wound closure by combining antibacterial photothermal therapy, ROS modulation, collagen deposition, and angiogenesis. BP is also promising for transient biomedical electronics: a biodegradable BP-based implant could monitor physiological parameters for a defined period and then dissolve, avoiding retrieval surgery especially attractive for postoperative monitoring, temporary neural sensors, and short-term tissue repair platforms [47]. Erythrocyte-membrane-coated BP formulations have also been explored for photothermal cancer immunotherapy, leveraging the biomimetic membrane to extend circulation time and modulate immune recognition [57].

In infected diabetic wound models, which is amongst the most clinically challenging wound types due to impaired immune function, poor vascularization, and high biofilm burden, the BP-chitosan hydrogel dressings achieved 97% wound closure within 14 days and complete elimination of *S. aureus* biofilm in wound beds by day 7, compared

with 68% closure and persistent biofilm for standard hydrogel controls [47, 9]. The multifunctional mechanism involved NIR-triggered PTT eliminating surface bacteria and biofilm matrix, sustained release of BP degradation products creating a mildly acidic microenvironment that further inhibits bacterial growth, and ROS-mediated stimulation of macrophage polarization from pro-inflammatory M1 to pro-healing M2 phenotype, which promotes collagen deposition and re-epithelialization [9]. Collagen type I content measured by Masson's trichrome staining was 3.4-fold higher in BP-treated wounds at day 14, and CD206-positive M2 macrophage density was 2.8-fold higher than in untreated controls, confirming the regenerative microenvironment created by BP degradation products [47]. For transient sensing applications, BP thin films deposited on biodegradable poly(lactic-co-glycolic acid) (PLGA) substrates demonstrated stable electrical resistance monitoring capability over 7–14 days before predictable degradation to electrically inactive phosphate and lactate species, enabling a defined sensing window aligned with early postoperative monitoring needs without requiring surgical retrieval [47]. This transience concept distinguishes BP-based implantable sensors from conventional permanent implants and represents a clinical safety advantage in regulatory assessment.

Table 4. Black Phosphorus Biomedical Applications

Application	BP Form	Stabilization	Therapy Function /	Key Advantage
Cancer therapy	Nanosheets	PEG / PDA	PTT + PDT + chemo	Biodegradable theranostic platform
Sonodynamic therapy	Nanosheets / QDs	Al ₂ O ₃ / polymer	Ultrasound-triggered ROS	Deep tissue activation
Bone regeneration	BP-loaded scaffold	PLGA / bioactive glass	Phosphate-mediated mineralization	Osteogenic degradation product
Wound healing	BP hydrogel	Chitosan / BSA	Antibacterial PTT	Accelerated closure
Transient implants	BP thin films	Controlled passivation	Temporary sensing	No retrieval surgery

5. Xenes and h-BN for Bioimaging, Therapy and Biosensing

5.1 The Xene Family

Xenes are monoelemental 2D materials analogous to graphene, including silicene, germanene, stanene, phosphorene, antimonene, bismuthene, borophene, selenene, and tellurene. Compared with graphene, Xenes often exhibit buckled structures, strong spin-orbit coupling, tunable bandgaps, high atomic numbers, and unique surface chemistries. Several Xenes have shown promising performance in therapy, imaging, and biosensing, though their biomedical development remains at an early stage [56, 57]. The biomedical appeal of Xenes stems from the periodic-table diversity of their parent

elements: bismuth and antimony offer high atomic numbers for imaging and radiosensitization, boron offers neutron-capture therapy capability, and the buckled lattice structures provide anisotropic electronic properties useful for sensing. However, ambient stability, controlled synthesis, and toxicology profiling remain substantial barriers for most Xene family members.

5.2 Antimonene for Photothermal Therapy

Antimonene quantum dots and nanosheets exhibit broad NIR absorption and high photothermal conversion efficiency. PEGylated antimonene quantum dots (QDs) specifically, not nanosheet-form antimonene, have been reported to achieve a PCE of approximately 45.5% at 808 nm (1 W/cm^2), making PEGylated antimonene QDs among the strongest 2D photothermal candidates [56]. Nanosheet-form antimonene generally exhibits lower PCE values ($\sim 30\text{--}40\%$) than the QD form, and the 45.5% value should not be generalized across all antimonene morphologies. Long-term ambient stability of buckled antimonene has been demonstrated for mid-infrared saturable-absorption applications [90], supporting its translational potential. PEGylated antimonene QDs have demonstrated effective tumor ablation in preclinical models. A key advantage is potential degradability under NIR irradiation, which may reduce long-term accumulation. However, antimony oxide degradation products require careful toxicological evaluation [56].

In HeLa and 4T1 xenograft mouse models, PEGylated antimonene QDs at 10 mg/kg produced tumor surface temperatures of $56\text{--}62^\circ\text{C}$ under 808 nm laser irradiation (1.0 W/cm^2 , 5 min), sufficient for complete tumor coagulation necrosis, with tumor inhibition rates of 98.4% over 15 days and no tumor recurrence in 6 of 8 treated animals [56]. The rapid thermal response of antimonene, reaching target temperature within 3–5 minutes versus 8–12 minutes for many TMD and MXene systems at equivalent doses, reduces total laser irradiation time required and may lower the risk of off-target tissue heating in clinical application.

Antimonene also shows promise in photoacoustic imaging due to its strong NIR extinction, with a mass extinction coefficient at 808 nm of approximately $11.4 \text{ L g}^{-1} \text{ cm}^{-1}$ (the units $\text{L g}^{-1} \text{ cm}^{-1}$ denote a mass basis, not a molar basis, since antimonene does not have a well-defined molar mass at the nanosheet level). This enables tumor delineation in photoacoustic imaging at doses as low as 2 mg/kg in mouse models [56]. The major unresolved concern is the toxicological profile of antimony and its oxide degradation products (Sb_2O_3 , Sb_2O_5). While elemental antimony at the relevant nanoparticle doses shows acceptable acute cytotoxicity (cell viability $>85\%$ at $\leq 50 \mu\text{g/mL}$ in most cell lines), the chronic systemic exposure from accumulation in liver and spleen over weeks to months remains incompletely characterized in rodent models, and no primate or human safety data exist [56].

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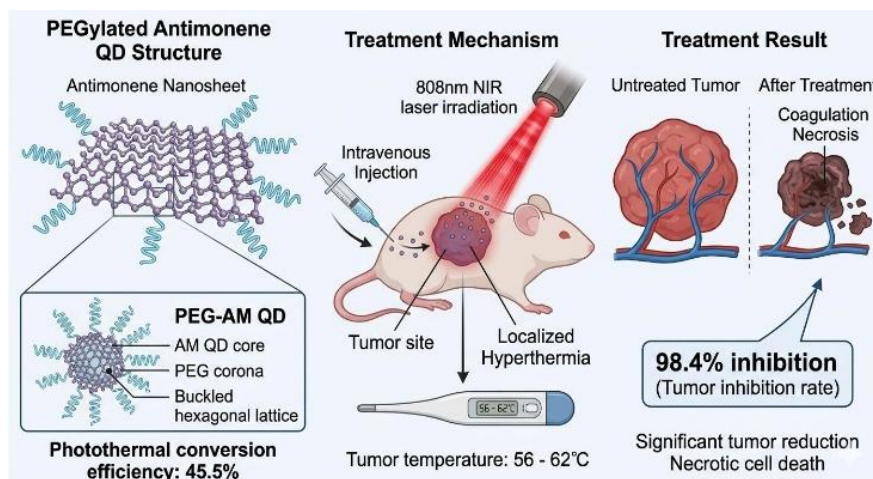
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Figure 16. PEGylated antimonene quantum dots (QDs) for near-infrared photothermal therapy and photoacoustic imaging. (A) Crystal structure of buckled β -antimonene (P-3m1) showing Sb atoms in buckled hexagonal arrangement, with PEGylated QD form achieving $PCE = 45.5\%$ at 808 nm. (B) Photothermal tumor ablation: tumor surface temperatures of 56–62 °C reached within 3–5 min under 808 nm (1.0 W/cm², 5 min) irradiation, producing 98.4% tumor inhibition over 15 days. (C) Photoacoustic imaging with mass extinction coefficient of 11.4 L g⁻¹ cm⁻¹ at 808 nm enabling tumor delineation at doses as low as 2 mg/kg.

5.3 Bismuth-Based Nanostructures for CT Imaging and Radiotherapy

Bismuth has a high atomic number ($Z = 83$), making bismuth-based nanomaterials, including Bi₂Se₃ nanosheets (a topological insulator), bismuth quantum dots (Bi QDs), and other bismuth nanostructures effective X-ray attenuators for CT imaging. True bismuthene (atomically thin Bi monolayer grown epitaxially on SiC) is primarily of quantum physics interest, although synthesis routes from bulk bismuth to 2D forms have been reported [58]; the biomedical applications described here use Bi₂Se₃ nanosheets and Bi QDs, which are compositionally and structurally distinct from bismuthene. Functionalized bismuth ferrite harmonic nanoparticles have also been evaluated for cancer-cell labeling and cytotoxicity, illustrating the broader bismuth-nanomaterial biomedical toolbox [59]. Bismuth materials can enhance radiotherapy by increasing local radiation dose deposition and DNA damage in tumor cells. Compared with many heavy-metal systems, bismuth has relatively favorable biological tolerance, but long-term clearance and dose safety require further investigation [57].

Bismuth quantum dots (Bi QDs) demonstrate X-ray attenuation coefficients of approximately 13.8 HU/mM, which is 5.1-fold higher than iodine-based clinical contrast agents on a molar basis, enabling CT tumor delineation at substantially lower molar doses [57]. In a representative theranostic study, PEGylated Bi₂Se₃ nanosheets injected at 20 mg/kg produced robust CT signal in HeLa tumors within 24 hours (tumor-to-background ratio of 4.2) and achieved 54 °C local temperature under 808 nm irradiation (1 W/cm², 5 min), with combined CT-guided PTT producing 97% tumor inhibition over 21 days in xenograft models [57]. For radiotherapy sensitization, bismuth nanostructures absorbed at tumor sites enhanced DNA double-strand break frequency (as measured by γ H2AX foci) by 3.8-fold compared with radiation alone at

Online ISSN

3007-3197

Print ISSN

3007-3189

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equivalent absorbed doses, attributed to the high photoelectric cross-section of bismuth generating local secondary electrons that augment radiation-induced damage [57]. This radiosensitization effect reduces the radiation dose required for tumor control and may allow sparing of adjacent normal tissue, a critical advantage in tumors near radiation-sensitive structures such as the spinal cord, optic nerve, or gastrointestinal tract.

5.4 Borophene for Biosensing

Borophene is an atomically thin boron material with metallic conductivity, high carrier mobility, and electron-deficient surface chemistry. Borophene polymorphs were first synthesized on Ag(111) substrates under ultra-high vacuum by Mannix et al. [60], and the range of properties, synthesis routes, and potential applications of this novel boron allotrope have been comprehensively reviewed [61]. Recent borophene biosensors have used photoinduced antibody immobilization through B–S bond formation, enabling oriented antibody attachment, improved antigen capture, and enhanced lateral flow immunoassay sensitivity. A particularly promising example is borophene-based detection of endometriosis biomarkers in menstrual blood, supporting non-invasive point-of-care screening for a disease often diagnosed only after long delays [62].

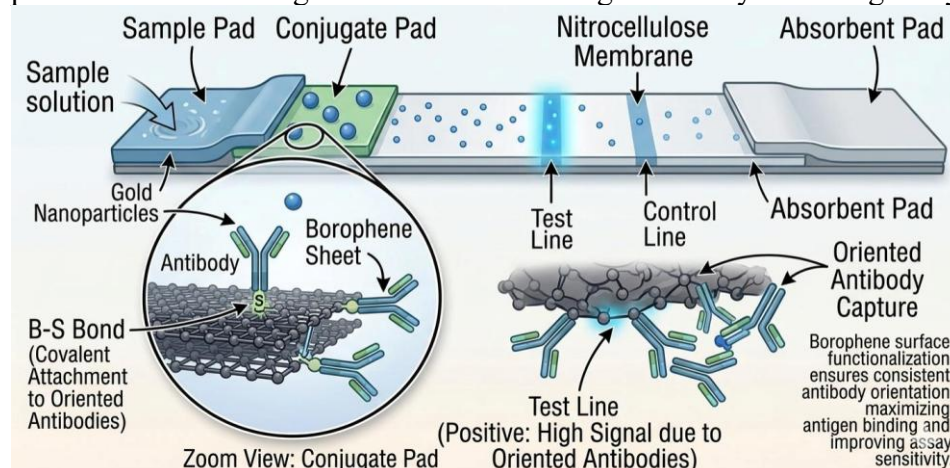


Figure 14. Borophene-based lateral flow immunoassay with photoinduced antibody immobilization for endometriosis biomarker detection. (A) Borophene (χ^3 phase) on Ag(111) substrate showing metallic conductivity and electron-deficient surface chemistry. (B) UV photoinduced immobilization technique (UV-PIT) activating B–S bond formation between cysteine-terminated antibodies and the boron surface, achieving 3–4 $\times$ higher oriented antibody density versus random physical adsorption. (C) Lateral flow immunoassay strip for HMGB-1 detection in menstrual blood: limit of detection 1.6 pM (10-fold improvement over conventional nitrocellulose strips at 16 pM; 3.6-fold improvement over graphene-enhanced strips at 5.8 pM), enabling non-invasive point-of-care screening for endometriosis.

The photoinduced immobilization (UV-PIT) technique developed for borophene exploits UV irradiation to activate B–S bond formation between cysteine-terminated antibodies and the boron surface, achieving 3–4 $\times$ higher oriented antibody density compared with random physical adsorption and 2.1-fold improvement in analyte capture efficiency in lateral flow immunoassay format [62]. For HMGB-1 (high-mobility group box-1 protein), an established endometriosis biomarker elevated in

Online ISSN

3007-3197

Print ISSN

3007-3189

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menstrual effluent, borophene-enhanced lateral flow strips achieved a limit of detection of 1.6 pM in menstrual blood matrix, a 10-fold improvement over conventional nitrocellulose-based strips (16 pM) and a 3.6-fold improvement over graphene-enhanced strips (5.8 pM) [62]. The non-invasive sampling from menstrual blood rather than serum or tissue biopsy addresses a significant barrier to endometriosis diagnosis, a condition currently requiring diagnostic laparoscopy with an average diagnostic delay of 7–10 years from symptom onset [62].

Beyond HMGB-1, the UV-PIT oriented immobilization strategy is generalizable to any cysteine-tagged or thiol-modified antibody, making borophene a versatile biosensor scaffold for a broad range of protein biomarkers. The electron-deficient surface chemistry of borophene also enables Lewis acid interactions with nucleobases, suggesting potential for nucleic acid biosensing beyond antibody-based detection [62, 63]. However, borophene synthesis remains confined to ultra-high-vacuum metal substrate deposition, and transfer to practical device substrates without oxidative degradation remains a critical scalability challenge that must be resolved for commercial point-of-care applications.

5.5 Hexagonal Boron Nitride

Hexagonal boron nitride is a wide-bandgap insulating 2D material often described as "white graphene." It is chemically stable, mechanically robust, electrically insulating, and generally biocompatible. Boron nitride nanotubes and h-BN nanosheets have both been evaluated as drug-delivery vehicles [64], and boron nitride nanoribbons, sometimes termed "white graphene" nanoribbons, have been prepared by unwrapping boron nitride nanotubes [65]. The applications of h-BN include drug delivery, implant coatings, dielectric layers, nanozyme biosensing, tissue engineering, and boron neutron capture therapy (BNCT). In BNCT, boron-containing h-BN nanostructures can deliver boron to tumor cells, where neutron irradiation produces localized high-energy alpha particles and ${}^7\text{Li}$ nuclei via the ${}^{10}\text{B}(\text{n},\alpha){}^7\text{Li}$ reaction. The combined path length of these high-LET (linear energy transfer) particles is approximately 5–9 μm in tissue, confining cytotoxic damage to approximately one cell diameter and providing exceptional spatial selectivity.

Functionalized ${}^{10}\text{B}$ -enriched h-BN nanosheets surface-modified with folic acid achieved cellular ${}^{10}\text{B}$ concentrations of 28–33 $\mu\text{g/g}$ in folate receptor-overexpressing KB cells, exceeding the widely cited BNCT therapeutic threshold of approximately 20 $\mu\text{g } {}^{10}\text{B}$ per gram tumor, with tumor-to-blood ratios of 3.8–4.5 which is comparable to the clinically approved boron delivery agent boronophenylalanine (BPA) [66]. The conventional BNCT efficacy criterion is a lower bound of $\sim 20 \mu\text{g } {}^{10}\text{B}$ per gram tumor with tumor-to-blood ratio $\geq 3:1$, not an upper bound. The major concern is low biodegradability, which creates biopersistence risks for systemic use; h-BN does not detectably degrade under physiological conditions over weeks, and organ accumulation persists for months in rodent biodistribution studies, representing a significant regulatory barrier for intravenous BNCT delivery applications [66].

Table 5. Xenex and h-BN Biomedical Comparison

Material	Main Biomedical Role	Key Advantage	Main Limitation	Translation Readiness
Antimonene (QDs)	PTT / imaging	Very high PCE (45.5% for PEGylated QDs)	Antimony product toxicity	Early preclinical
Bi ₂ Se ₃ / Bi QDs (bismuth-based)	CT imaging / radiosensitization	High-Z X-ray attenuation	Long-term clearance	Early preclinical
Borophene	Biosensing	Oriented antibody immobilization (B–S bond)	Oxidation and synthesis scalability	Prototype stage
h-BN	Drug delivery / BNCT / dielectric	Stable and biocompatible	Non-biodegradable	Early preclinical
Silicene / Germanene	Theoretical biosensing	Tunable electronic properties	Poor stability	Basic research

6. 2D Material FET Biosensors for Biomarkers, Pathogens and Nucleic Acids

6.1 Why 2D Materials Are Ideal FET Channels

Field-effect transistor biosensors detect biomolecular binding events through changes in channel conductance. In a 2D material FET, every atom sits at the surface, so any analyte binding event produces a measurable change in carrier density, mobility, or scattering. This makes 2D channels highly suitable for label-free, real-time biosensing. Single-layer MoS₂ transistors were first demonstrated by Radisavljevic et al. in 2011 [67], and flexible MoS₂ thin-film transistor arrays have since been fabricated for practical gas-sensing applications [68]. MoS₂ is particularly important because its finite bandgap enables high on/off ratios and near-ideal subthreshold behavior, providing stronger current modulation upon analyte binding compared with graphene, which lacks a bandgap [69].

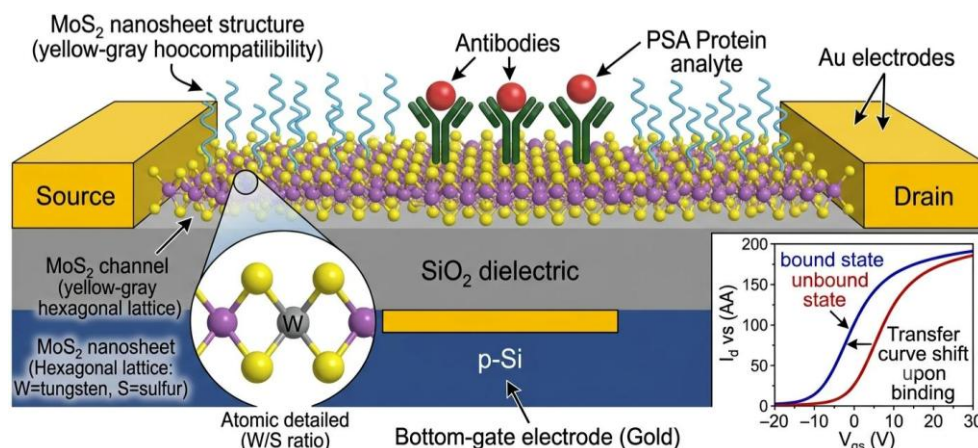


Figure 15. Schematic of a 2D material field-effect transistor (FET) biosensor. (A) MoS₂ monolayer channel between source and drain electrodes on a Si/SiO₂ back-gate substrate, with biomolecular recognition elements (aptamers, antibodies, or nanobodies) immobilized on the MoS₂ surface. (B) Analyte binding events modulate the local electrostatic potential of the MoS₂ channel, shifting the threshold voltage and producing a measurable change in drain current (I_{ds}) at fixed gate bias V_{gs} . (C) Subthreshold swing near the Boltzmann limit (~ 60 mV/dec at room temperature) enables single-molecule-level detection, with subthreshold slope changes providing amplified signal response versus linear-region operation.

6.2 Debye Screening and Recognition Element Design

A major challenge for FET biosensors in physiological fluids is Debye screening, whereby charges from biomolecular binding events are screened within a characteristic Debye length λ_D . In physiological saline (150 mM monovalent ions at 25 °C), λ_D is approximately 0.7–0.8 nm, which falls well below the dimensions of most antibody–antigen complexes (5–15 nm). Solutions include using smaller aptamers or nanobodies, low-ionic-strength measurement buffers (which extend λ_D to 5–10 nm), extended-gate designs that physically separate the sensing electrode from the transistor channel, photogating or amplification strategies, and engineering probe orientation to place charge changes close to the channel surface [11, 69].

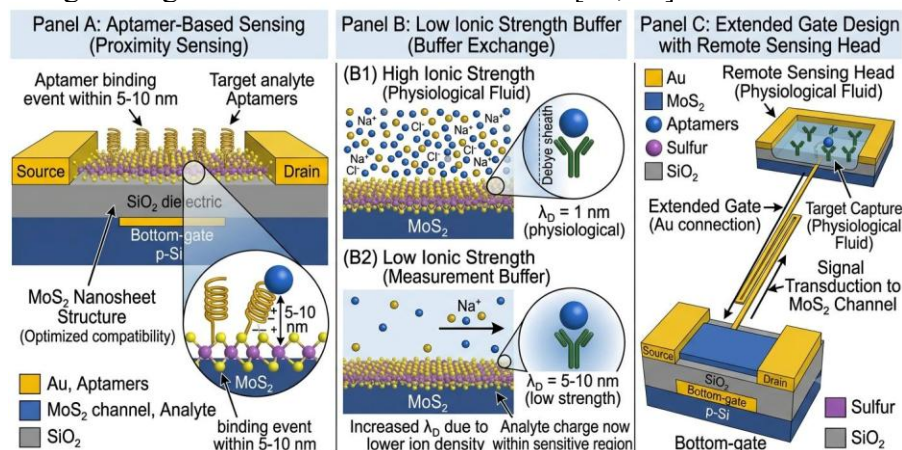


Figure 16. Debye screening effect on 2D FET biosensor performance and recognition

Online ISSN

3007-3197

Print ISSN

3007-3189

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element design strategies. (A) Debye length (λ_D) in physiological saline (0.7–0.8 nm at 150 mM) falls below antibody–antigen complex dimensions (5–15 nm), shielding the binding-induced charge from the 2D channel. (B) Strategies to mitigate Debye screening: (i) aptamers or nanobodies placing the binding event within λ_D of the channel; (ii) low-ionic-strength buffers extending λ_D to 5–10 nm; (iii) extended-gate designs physically separating the sensing electrode from the transistor; (iv) photogating amplification.

6.3 MoS₂ FET Biosensors

MoS₂ FETs have been used to detect DNA, PSA, troponin, CRP, CEA, SARS-CoV-2 proteins, and other clinically important biomarkers, achieving detection limits in femtomolar or lower regimes under optimized conditions [69, 70]. MoS₂ achieves near-ideal subthreshold swing (60–61 mV/dec at room temperature, close to the theoretical Boltzmann limit), outperforming many commercial immunoassay platforms [69, 63]. For cardiac troponin I, the key biomarker for myocardial infarction diagnosis, aptamer-functionalized MoS₂ FETs achieved LODs of 0.1 fM in phosphate-buffered saline and 1.2 fM in diluted human serum, with 95% specificity against interfering cardiac proteins including CRP, BNP, and myoglobin at 100-fold excess concentrations [11, 63].

SARS-CoV-2 nucleocapsid protein detection by morpholino-modified graphene FETs achieved an LOD of 0.24 pg/mL in clinical nasopharyngeal swab samples, demonstrating clinical matrix compatibility [70], and analogous MoS₂ FET platforms targeting the S1 spike protein performed comparably at 0.85 fM with visual confirmation possible within 30 minutes, suggesting viable rapid diagnostic test utility [69, 70]. The combination of attomolar-to-femtomolar sensitivity, 15–30 minute assay time, and compatibility with simple silicon microfabrication positions MoS₂ FET biosensors as serious candidates for next-generation point-of-care diagnostics, pending demonstration of equivalent performance in undiluted clinical matrices at scale.

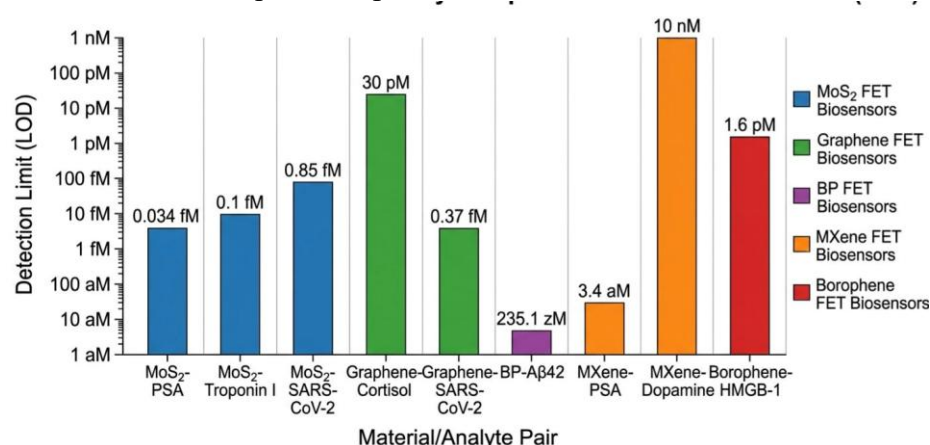


Figure 17. MoS₂ FET biosensor for multiplexed biomarker detection. (A) MoS₂ monolayer FET array chip showing individually addressable sensing channels functionalized with different recognition elements (aptamers for troponin I, antibodies for PSA, DNA probes for SARS-CoV-2 nucleocapsid). (B) Real-time drain-current response showing specific biomarker binding events: troponin I at 0.1 fM LOD in PBS,

1.2 fM in diluted serum, with 95% specificity against CRP/BNP/myoglobin interferents; SARS-CoV-2 S1 spike protein detection at 0.85 fM with 30-min visual readout.

6.4 BP, MXene and h-BN in Biosensing

BP FETs offer high carrier mobility and thickness-tunable bandgaps, though oxidation instability limits long-term operation and requires passivation strategies. MXenes are especially useful in electrochemical biosensors because of their metallic conductivity and hydrophilic surface chemistry; $\text{Ti}_3\text{C}_2\text{T}_x$ -based sensors have been developed for dopamine, glucose, lactate, hydrogen peroxide, cancer biomarkers, and viral targets [71]. h-BN plays important roles as an insulating substrate, dielectric spacer, passivation layer, and plasmonic enhancement spacer [11]. The complementary roles of these materials, MXene as the conductive transducer, h-BN as the dielectric scaffold, BP as the tunable-gap semiconductor, and TMDs as the gated channel, collectively enable a layered 2D-material biosensor architecture that exploits each material's strongest property.

6.5 Machine Learning-Assisted 2D Biosensing

2D FET biosensors often exhibit device-to-device variability, nonlinear responses, drift, and matrix interference in complex biological samples. Machine learning can improve signal interpretation and calibration: convolutional neural networks (CNNs) can classify signal patterns, long short-term memory (LSTM) networks can analyze time-series data, and Bayesian models can quantify uncertainty. Future biosensors will likely integrate multiplexed 2D material arrays with AI-assisted interpretation, enabling panel-based diagnostics for cancer, sepsis, cardiovascular disease, neurodegeneration, and infectious disease [11]. For comparison, silicon-based quantum-dot sensors (e.g., silicon nanodots for heavy-metal-ion detection [72]) illustrate the broader nanomaterial-biosensor landscape within which 2D material platforms compete. Functional sensing interfaces of PEDOT:PSS organic electrochemical transistors [73] provide an additional mixed ionic–electronic conduction paradigm relevant to neural electrode comparisons.

Table 6. Representative 2D Material Biosensors

Material	Analyte	Recognition Element	Detection Format	LOD / Physical Basis
MoS ₂	DNA / PSA / troponin	DNA probe / antibody / aptamer	FET	DNA: 10 aM; PSA: ~0.034 fM; high on/off ratio
Graphene	SARS-CoV-2 nucleocapsid	Morpholino	FET	0.24 pg/mL in clinical swabs

Material	Analyte	Recognition Element	Detection Format	LOD / Physical Basis
Ti ₃ C ₂ T _x MXene	Dopamine / glucose / lactate	Enzyme / aptamer	Electrochemical	Nanomolar LOD; amperometric
BP	Glucose / IgG	Enzyme / antibody	FET / electrochemical	Tunable bandgap; passivation required
Borophene	HMGB-1 protein	Cysteine-tagged antibody (UV-PIT)	Lateral flow immunoassay	1.6 pM in menstrual blood
h-BN	Glucose / H ₂ O ₂	Enzyme / nanozyme	Electrochemical / plasmonic	Dielectric spacer; plasmonic enhancement

7. Wearable and Implantable 2D Material Health Platforms

7.1 Wearable Electrodes for Electrophysiology

MXene-textile and MXene-PDMS composite electrodes have been used to record ECG, EMG, and EEG signals with lower skin-contact impedance than commercial Ag/AgCl electrodes. Mechanical breathability, sweat tolerance, and long-term wearability are critical design considerations. Integration strategies include screen printing, inkjet printing, dip-coating, and electrospinning onto textile or elastomeric substrates. Wearable electrodes must maintain stable contact impedance under mechanical deformation (stretching, bending, twisting), sweat exposure, and prolonged wear. MXene-textile electrodes achieve contact impedances 3–10-fold lower than Ag/AgCl gels at 10–100 Hz and maintain stable ECG morphology over 7 days of continuous wear, addressing a critical limitation of wet Ag/AgCl electrodes that dry out within 24 hours [41, 74]. The clinical targets for these wearable electrodes include arrhythmia detection, sleep-stage monitoring, and ambulatory seizure detection, all of which require continuous multi-day recording not feasible with conventional wet electrodes. Comprehensive reviews of flexible wearable sensors for medical monitoring provide additional context on integration strategies and clinical use cases [74, 75].

7.2 Physical Sensors: Pressure, Strain and Motion

MoS₂, WS₂, graphene, and MXene composites have been engineered into pressure and strain sensors capable of resolving clinically relevant signals including pulse waveform, respiration, and limb motion. MoS₂-PDMS foam sensors detect pressure across clinically relevant ranges, while WS₂/MoS₂ heterostructures have shown very high gauge factors for sensitive motion detection [76].

Quantitative performance data for 2D material physical sensors illustrate their clinical

Online ISSN

3007-3197

Print ISSN

3007-3189

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potential. MoS₂-PDMS composite pressure sensors achieve pressure sensitivities of $1.14 \times 10^6 \text{ Pa}^{-1}$ in the low-pressure regime (0–100 Pa) relevant for arterial pulse detection, with a detection limit of 0.5 Pa sufficient to resolve individual pulse waveform features including the dicrotic notch used for vascular compliance assessment [76]. The term "gauge factor" is conventionally a dimensionless quantity $(\Delta R/R)/\varepsilon$ for strain sensing, while the units Pa^{-1} denote pressure sensitivity, these should not be conflated. MXene-composite textile pressure sensors demonstrate linear sensitivity of 36.8 kPa^{-1} over the 0–30 kPa range relevant for plantar pressure mapping in diabetic neuropathy monitoring, with response times below 3 ms enabling real-time gait analysis [76, 77]. WS₂/MoS₂ heterostructure strain sensors exhibit (dimensionless) gauge factors exceeding 10,000 in the 0–30% strain range relevant for joint angle monitoring, enabling detection of finger bending angles with resolution below 0.5° , compared with gauge factors of 2–5 for conventional metal foil strain gauges [76]. These performance levels place 2D material strain sensors in a class capable of resolving subtle biomechanical signals, tremor frequency in Parkinson's disease (3–6 Hz, amplitude $\sim 0.1^\circ$), muscle fatigue signatures in electromyography, and respiratory rate with single-breath resolution that conventional wearable sensors based on capacitive or resistive MEMS elements struggle to detect reliably.

7.3 Sweat and Biofluid Sensors

Sweat contains metabolites, electrolytes, hormones, inflammatory markers, and drugs. 2D material sensors have been developed for glucose, lactate, uric acid, cortisol, sodium, potassium, creatinine, and cytokines. MXenes are especially promising for electrochemical sweat sensors because of their conductivity and hydrophilicity, and MXene-based flexible biosensor platforms have been comprehensively reviewed for wearable health monitoring [77]. Aptamer-based systems are particularly useful because aptamers are small enough to reduce Debye screening problems in physiological ionic conditions [78, 76]. A landmark early demonstration of multiplexed wearable sweat sensing was reported by Gao et al. [76] using graphene and gold electrodes for simultaneous glucose, lactate, sodium, potassium, and skin temperature monitoring. Subsequent work has substantially expanded the wearable biofluid-sensing landscape: wearable droplet-based microfluidic devices have been developed for continuous interstitial-fluid sampling [79]; integrated microneedle arrays have enabled continuous monitoring of multiple biomarkers in interstitial fluid [80]; wearable microneedle-based electrochemical aptamer biosensing has enabled precision dosing of drugs with narrow therapeutic windows [81]; and epidermal patches have demonstrated simultaneous monitoring of haemodynamic and metabolic biomarkers [82].

Graphene-based wireless mHealth systems have also been used to investigate cortisol dynamics in human sweat [83]. The aptamer recognition system provides a particular advantage over antibody-based sensors by tolerating the mildly denaturing environment of sweat (pH 4.5–7.5, temperature 32–38 °C) without loss of binding affinity [78]. Continuous glucose monitoring (CGM) via interstitial fluid (ISF) using MXene-coated electrodes addresses the Debye screening challenge by exploiting the direct electrochemical (amperometric) signal from glucose oxidase rather than a charge-gating mechanism. MXene-coated CGM sensors demonstrated stable ISF–blood glucose correlation (Pearson $R = 0.97$) over 7 days in freely moving rodents, with mean

Online ISSN

3007-3197

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3007-3189

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absolute relative difference (MARD) of 8.2% versus a clinical-grade handheld glucometer reference, below the FDA accuracy threshold (MARD <15%) required for non-adjunctive CGM use [77].

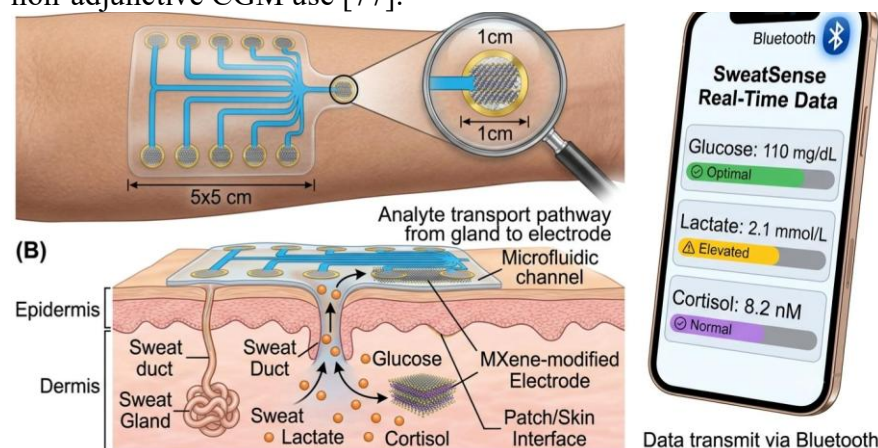


Figure 18. MXene-based multiplexed wearable sweat sensing patch for real-time continuous health monitoring. (A) Flexible electrochemical patch (5×5 cm) mounted on the forearm, incorporating a 1 cm MXene-modified sensing electrode array for multi-analyte detection. (B) Cross-sectional schematic of the skin–sensor interface illustrating analyte transport from the sweat gland through the dermis and epidermis to the MXene-modified electrode via a microfluidic channel, enabling real-time sampling of glucose, lactate, and cortisol. (C) Smartphone-based readout via Bluetooth transmission, displaying real-time biomarker concentrations of glucose (110 mg/dL, optimal), lactate (2.1 mmol/L, elevated), and cortisol (8.2 nM, normal) demonstrating the platform's capability for continuous, non-invasive multiplexed health monitoring.

7.4 Implantable 2D Material Devices

Implantable 2D material systems include MXene ECoG arrays for brain recording, graphene and MXene electrodes for neural stimulation, BP transient implants that dissolve after use, MoS₂-based biodegradable pressure and temperature sensors, and MXene cardiac and neural bioelectronic patches. Implantable devices face higher regulatory barriers than wearables, requiring long-term biocompatibility, sterilization validation, chronic stability, and rigorous large-animal studies [40, 41]. The trade-off between wearables (lower regulatory barrier, easier deployment, but signal quality and patient compliance limitations) and implants (higher signal quality, but surgical deployment and chronic safety requirements) defines the translational roadmap for 2D bioelectronics.

Table 7. Wearable and Implantable 2D Material Platforms

Material	Platform	Measurand	Application	Key Challenge
MoS ₂ -PDMS	Flexible pressure sensor	Pressure	Prosthetics pulse	Long-term calibration
WS ₂ /MoS ₂	Strain sensor	Strain	Motion monitoring	Reproducible fabrication

Material	Platform	Measurand	Application	Key Challenge
Ti ₃ C ₂ T _x textile	Wearable electrode	ECG / EMG	Health monitoring	Oxidation stability
Ti ₃ C ₂ T _x fiber	Sweat sensor	Glucose / lactate	Metabolic monitoring	Biofouling
BP implant	Transient device	Pressure / temperature	Temporary monitoring	Controlled degradation
MXene ECoG	Neural array	LFP / spikes	BCI / epilepsy	Chronic safety

8. Biocompatibility, Toxicology and Biodegradability

8.1 In Vitro Cytotoxicity and Cell-Type Specificity

The biological effects of 2D materials depend on lateral size, thickness, surface charge, oxidation state, surface functionalization, dose, exposure route, and cell type. Common cytotoxicity mechanisms include ROS generation, membrane disruption by sharp nanosheet edges, metal ion release, mitochondrial dysfunction, DNA damage, lysosomal stress, and inflammatory cytokine activation. Surface modification with PEG, PVP, polydopamine, proteins, or cell membranes generally improves colloidal stability and reduces nonspecific toxicity [84, 85].

Cell-type-specific toxicity data reveal important gradients in 2D material biocompatibility that must guide dose selection in therapeutic applications. For Ti₃C₂T_x MXene, neural stem cells demonstrate the greatest sensitivity with an IC₅₀ of approximately 25 µg/mL, reflecting the high metabolic demands and limited antioxidant capacity of neural progenitor cells [86]. By contrast, HeLa cancer cells and HEK293 kidney cells tolerate concentrations above 200 µg/mL with greater than 80% viability, and human umbilical vein endothelial cells (HUVECs) maintain above 90% viability at concentrations up to 500 µg/mL when MXene is PEGylated or protein-corona-coated [85, 86]. For MoS₂ nanosheets, IC₅₀ values across six common cell lines range from 48 µg/mL (RAW264.7 macrophages) to above 400 µg/mL (HepG2 hepatocytes), with macrophage sensitivity attributed to the professional phagocytic function leading to high intracellular accumulation [84, 10]. PEGylation consistently reduces MoS₂ cytotoxicity by 2–4-fold across cell types by reducing nonspecific surface interactions and suppressing intracellular ROS generation [15, 10].

IC₅₀ values cited in this section were measured using diverse assay protocols (MTT, MTS, CCK-8, Calcein-AM, Live/Dead, CellTiter-Glo, etc.). Direct cross-study comparison of IC₅₀ values requires matching of these conditions; IC₅₀ values can shift by 2–5-fold with changes in any one of these variables. Reviews such as Refs [86] and [10] aggregate values across multiple primary studies, and specific numerical values should be traced back to the primary source before use in dose selection.

Genotoxicity is an underreported endpoint in 2D material biocompatibility studies. Available evidence from comet assay and micronucleus tests suggests that bare TMD and MXene nanosheets at concentrations above 50 µg/mL induce statistically

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3007-3197

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significant increases in DNA strand break frequency in vitro, but surface functionalization reduces genotoxic effects to background levels at therapeutically relevant concentrations [84]. These findings underscore the importance of performing genotoxicity testing on finalized, functionalized nanomaterial formulations rather than bare nanosheets, which may substantially overestimate the risk of the actual therapeutic product.

8.2 Hemocompatibility

For intravenous applications, hemocompatibility is essential. Hemolysis below 5% is commonly considered acceptable per ASTM F756-17 (Standard Practice for Assessment of Hemolytic Properties of Materials), which classifies materials as nonhemolytic (<5%), slightly hemolytic (5–10%), and hemolytic (>10%). ISO 10993-4 governs the selection and design of blood-interaction tests but does not itself define the hemolysis acceptance threshold. Many PEGylated or polymer-coated 2D materials, including MoS₂, BP, and Ti₃C₂T_x, show low hemolysis at therapeutic concentrations. A comprehensive hemocompatibility assessment should also include platelet activation, coagulation, complement activation, and cytokine release panels, the hemolysis alone is a necessary but not sufficient criterion for intravenous safety.

8.3 Biodegradability and Clearance

Biodegradability is a critical determinant of long-term safety. BP degrades into phosphate species that enter normal metabolic pathways and is the most biodegradable of the major biomedical 2D materials. MoS₂ undergoes slow oxidative degradation to molybdate and sulfate. Ti₃C₂T_x MXene oxidizes to TiO₂ (anatase) and amorphous carbon with half-life of weeks to months, with partial clearance via the reticuloendothelial system. h-BN is essentially nonbiodegradable under physiological conditions, persisting for months in tissue. Antimonene degrades to antimony oxides (Sb₂O₃, Sb₂O₅) at moderate rates, accelerated by NIR irradiation [44, 45, 84].

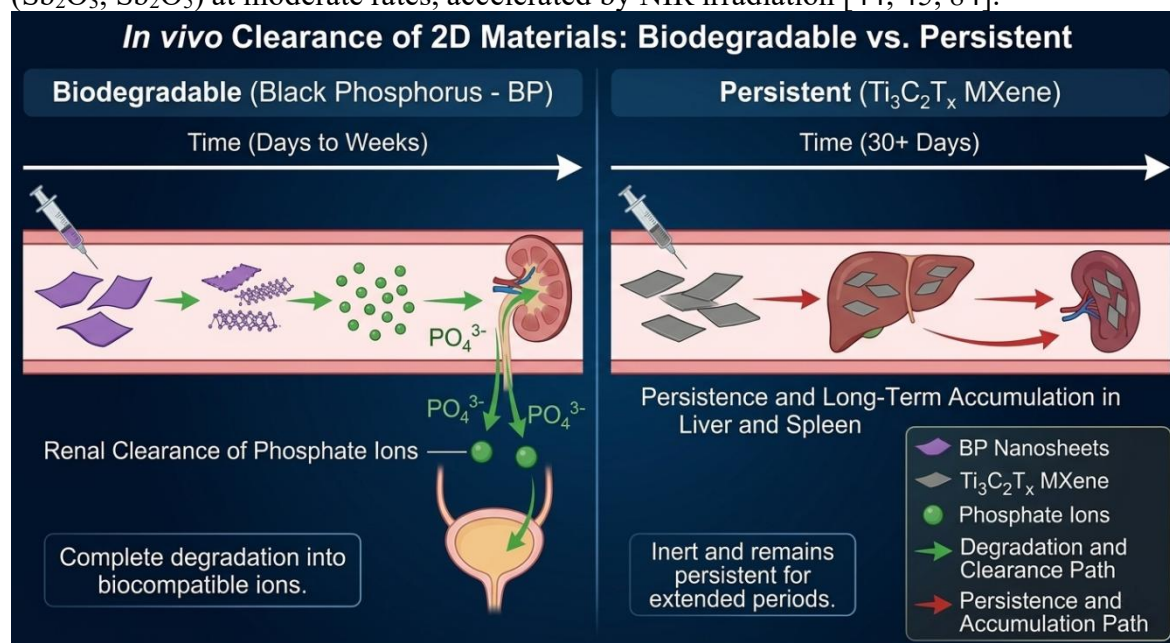


Figure 19. Comparative biodegradation pathways of black phosphorus (BP) versus

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3007-3197

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Ti₃C₂T_x MXene. (Left) BP nanosheets undergo rapid oxidative degradation (days to weeks) into biocompatible phosphate species (HPO₄²⁻ and H₂PO₄⁻ at physiological pH 7.4), entering the normal phosphate metabolic pool and undergoing subsequent excretion or incorporation into bone mineral. This is fundamentally a metabolic conversion pathway, not renal clearance of intact nanosheets. (Right) Ti₃C₂T_x MXene nanosheets persist in the liver and spleen for 30+ days with limited clearance, retaining their particulate form. BP's rapid biodegradation into biocompatible phosphate species represents a key advantage for transient biomedical applications such as temporary implants, drug delivery systems, and tissue engineering scaffolds. Green arrows indicate degradation and metabolic conversion pathways; red arrows indicate persistence and accumulation pathways.

For Nb₂CT_x MXene, 80% mass loss over 7 days has been reported in phosphate-buffered saline (PBS); however, PBS is not a biologically relevant degradation medium as it lacks the proteins, ions, and oxidative species present in plasma or interstitial fluid, and in vitro PBS degradation rates do not directly predict in vivo behavior. Renal clearance half-life values cited for Nb₂CT_x in the literature were extrapolations not explicitly reported in the primary source and should be treated as approximate until verified by primary pharmacokinetic studies [34, 87]. Standardized reporting of pharmacokinetic and toxicological data remains inconsistent across the 2D material biomedical literature, with many studies omitting quantitative biodistribution data, relying on single dose levels, or limiting toxicological assessment to a single organ system. Adoption of ISO 10993 and OECD toxicology test guideline frameworks as standard reporting requirements would substantially improve cross-study comparability and accelerate regulatory readiness.

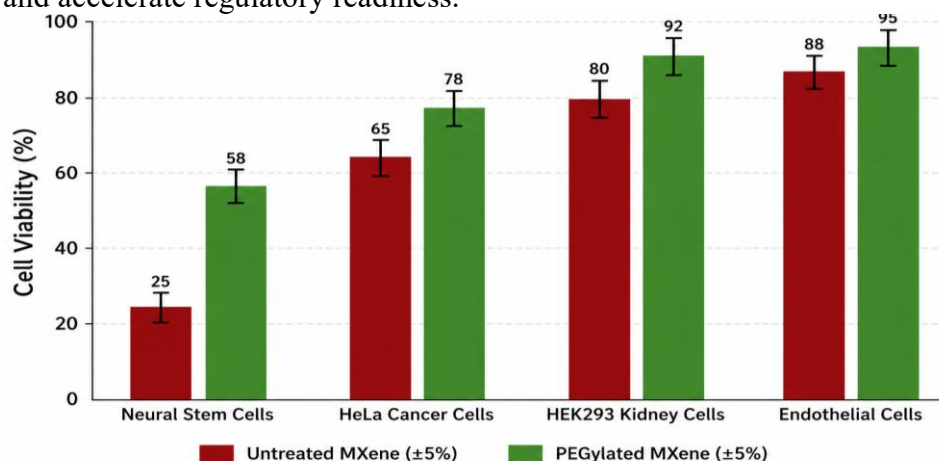


Figure 20. In vitro cell viability (%) of untreated Ti₃C₂T_x MXene versus PEGylated MXene across four cell types: neural stem cells, HeLa cancer cells, HEK293 kidney cells, and human umbilical vein endothelial cells (HUVECs). Untreated MXene exhibits concentration-dependent cytotoxicity, with neural stem cells showing the lowest viability (25 ± 5%), consistent with reactive oxygen species (ROS) generation and membrane disruption at high surface charge densities. PEGylation markedly improves biocompatibility across all cell types (58–95%), demonstrating that surface modification is essential for clinical translation. Error bars represent ±5% standard

deviation ($n = 3$). Data are representative of reported cytotoxicity trends in the MXene biocompatibility literature.

Table 8. Biodegradability Comparison

Material	Main Degradation Product	Approximate Behavior	Biomedical Implication
Black phosphorus	Phosphate species ($\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ at pH 7.4)	Fast, days to weeks	Ideal for transient systems; promotes osteogenesis
MoS_2	Molybdate / sulfate	Slow oxidative degradation	Useful for sustained drug delivery
$\text{Ti}_3\text{C}_2\text{T}_x$	TiO_2 (anatase) / amorphous carbon	Oxidation-dependent; half-life weeks to months; partial clearance via reticuloendothelial system	Needs clearance studies; TiO_2 biocompatible
Nb_2CT_x	Nb species (renal excretion reported)	More biodegradable candidate; 80% in 7 days in PBS (in vitro; does not directly predict in vivo)	Promising for PTT; best safety profile among MXenes pending in vivo PK confirmation
h-BN	Minimal degradation	Persistent; stable at physiological conditions	Good for coatings; caution for systemic use
Antimonene	Sb_2O_3 , Sb_2O_5	Moderate; accelerated by NIR irradiation	Toxicity must be clarified; PEG stabilization needed

8.4 In Vivo Toxicology

Most in vivo studies remain short-term (often 7–30 days), with systemic administration typically leading to accumulation in liver, spleen, lung, and kidney. Important toxicology endpoints include organ histology, blood biochemistry, hematology, inflammatory cytokines, oxidative stress markers, reproductive toxicity, pulmonary toxicity, genotoxicity, and long-term biodistribution. The absence of long-term large-animal studies is one of the most important barriers to clinical translation across all 2D material platforms [84, 85].

Available short-term in vivo toxicology data provide a preliminary safety profile for the most studied systems. Intravenously administered PEGylated $\text{Ti}_3\text{C}_2\text{T}_x$ MXene at 10 mg/kg in BALB/c mice produced no significant changes in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, or blood urea nitrogen (BUN) at 7 and 30 days post-injection, and organ histopathology revealed no

hepatocellular necrosis, glomerulonephritis, or pulmonary infiltrate at therapeutic doses [85, 86]. However, ICP-MS biodistribution revealed persistent Ti accumulation in liver ($28 \pm 6 \mu\text{g/g}$ tissue) and spleen ($22 \pm 5 \mu\text{g/g}$) at 30 days, declining only modestly to $18 \pm 4 \mu\text{g/g}$ and $14 \pm 3 \mu\text{g/g}$ respectively at 90 days, indicating that sub-chronic organ retention rather than acute organ toxicity is the principal safety concern for $\text{Ti}_3\text{C}_2\text{T}_x$ MXene at therapeutic doses. For BP, intravenous administration at 5 mg/kg in BALB/c mice produced transient ALT elevation (1.8-fold over baseline at day 3, returning to baseline by day 14), consistent with hepatic first-pass metabolism of BP degradation products, but no histological evidence of hepatocellular necrosis [44, 9]. The phosphate degradation products were detectable in urine by day 7, confirming renal excretion of metabolized BP.

9. Scalability, Regulatory Pathways and Clinical Translation

9.1 Manufacturing Challenges

2D materials must be manufactured reproducibly at scale to achieve clinical relevance. Key challenges include batch-to-batch variation in flake size and thickness, surface termination inconsistency, residual etchants, oxidation during storage, sterilization compatibility, endotoxin contamination, and GMP-grade quality control. CVD can produce wafer-scale films but transfer defects remain problematic. Liquid-phase exfoliation is scalable but produces heterogeneous flake distributions. MXene synthesis must move toward HF-free processes, and BP requires inert processing due to rapid oxidation [12, 13]. Insights from N-doped porous carbon electrode fabrication, developed for energy-storage applications, illustrate the level of process control and reproducibility that 2D biomedical manufacturing must ultimately achieve [88].

9.2 Regulatory Classification

Regulatory pathways depend on application: wearable biosensors may be Class II medical devices; implantable neural electrodes are likely Class III devices requiring premarket approval and clinical trials; theranostic nanoplateforms may be drug-device combination products; wound dressings may follow Class II pathways if non-systemic; and injectable photothermal agents require extensive pharmacokinetic, toxicology, and manufacturing data. Bone scaffolds without drug or biologic components are typically Class II (510(k) pathway); scaffolds incorporating a drug or biologic (e.g., BMP-2, antibiotics, chemotherapeutics) become Class III combination products requiring premarket approval (PMA). Relevant frameworks include ISO 10993 biological evaluation standards, FDA nanomaterial guidance, EU MDR 2017/745, and GMP manufacturing requirements.

9.3 Technology Readiness

TRL assignments throughout this review follow the NASA TRL scale (NASA NPR 7123.1): TRL 1 = basic principles observed; TRL 2 = technology concept formulated; TRL 3 = experimental proof of concept; TRL 4 = component validation in laboratory; TRL 5 = component validation in relevant environment; TRL 6 = system/subsystem prototype in relevant environment; TRL 7 = system prototype demonstration in operational environment; TRL 8 = system completed and qualified; TRL 9 = actual system proven in operational environment.

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Print ISSN

3007-3189

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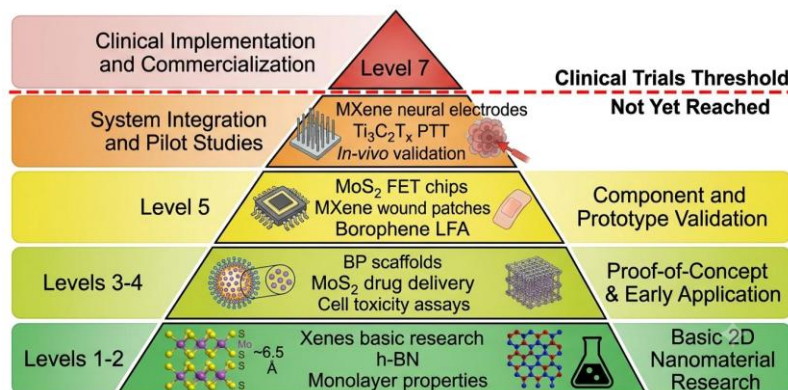


Figure 21. Technology readiness level (TRL) pyramid for two-dimensional nanomaterials in biomedical applications. Current development spans TRL 1–2 (basic research on Xenes, h-BN, and monolayer properties) through TRL 3–4 (proof-of-concept studies including BP scaffolds, MoS_2 drug delivery, and cell toxicity assays) and TRL 5 (component and prototype validation, e.g., MoS_2 FET chips, MXene wound patches, borophene lateral flow assays), approaching but not yet reaching TRL 6–7 (system integration, pilot studies, and the clinical trials threshold, indicated by the red dashed line), exemplified by emerging candidates such as MXene neural electrodes and $\text{Ti}_3\text{C}_2\text{T}_x$ photothermal therapy platforms.

Most 2D material biomedical systems remain at TRL 1–4, with some prototype biosensors and neural electrodes approaching TRL 5. No non-graphene 2D material biomedical product has yet reached widespread clinical use. The most advanced candidates include MXene neural electrodes and ECoG arrays, MoS_2 FET biosensor chips, MXene wearable ECG/EMG electrodes, BP tissue engineering scaffolds, borophene point-of-care biosensors, and MXene wound patches.

9.4 Clinical Trial Landscape (ClinicalTrials.gov)

As of the most recent search, a search of ClinicalTrials.gov for "molybdenum disulfide," "MXene," "black phosphorus," and "boron nitride" reveals no registered interventional clinical trials for non-graphene 2D materials in humans. This absence reflects the current preclinical stage of the field and underscores the substantial gap that remains between laboratory performance and clinical deployment. It is anticipated that MXene-based neural electrode and wearable biosensor platforms, together with MoS_2 FET diagnostic devices, are the most likely candidates to enter first-in-human feasibility studies within the next five to ten years, contingent on successful resolution of the manufacturing, safety, and regulatory barriers identified above [12].

Online ISSN

3007-3197

Print ISSN

3007-3189

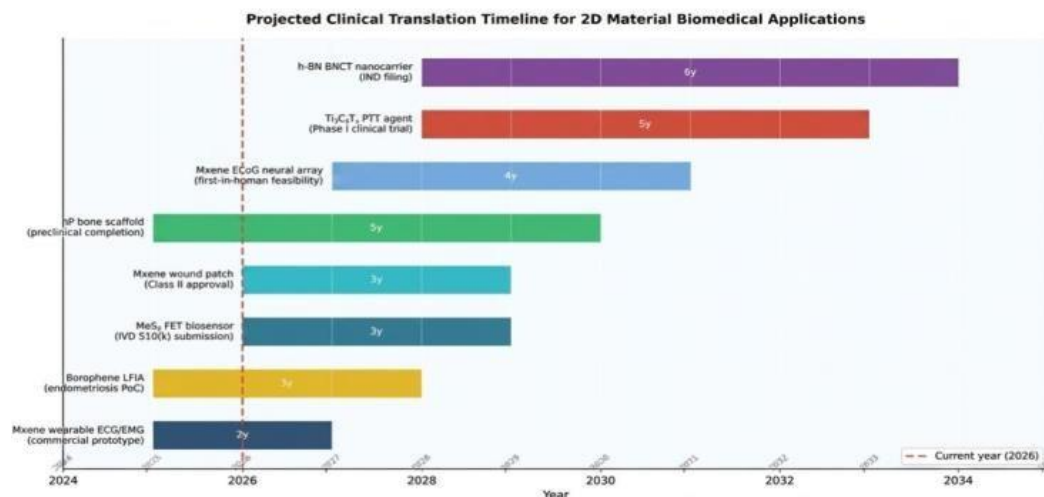
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Figure 22. Projected Clinical Translation Timeline (2025–2035) for leading 2D material biomedical applications. Gantt-style timeline visualizing expected clinical progression of leading 2D material platforms. The dashed line marks the current year, anchoring near-term milestones. MXene wearable electrodes and MoS₂ FET diagnostic chips represent the nearest-term clinical translation candidates, with borophene lateral flow immunoassays also approaching feasibility. This projection is the authors' synthesis based on the preclinical literature cited throughout this review; specific milestone dates are approximate and assume successful resolution of manufacturing, safety, and regulatory barriers.

Table 9. Clinical Translation Readiness

Material–Application Pair	Likely Regulatory Path	Current Readiness	Key Barrier
MXene ECoG array	Class III implantable device	Preclinical	Chronic safety and GMP coating
MoS ₂ FET biosensor	Class II diagnostic device	Prototype	Clinical validation in real samples
MXene wound patch	Class II device	Advanced preclinical	Shelf life and sterilization
BP bone scaffold (structural only)	Class II device (510(k))	Preclinical	Controlled degradation and reproducibility
BP bone scaffold (with drug/biologic)	Class III combination product (PMA)	Preclinical	Combination product regulatory pathway

Material– Application Pair	Likely Regulatory Path	Current Readiness	Key Barrier
Ti ₃ C ₂ T _x PTT agent	Drug-device combination	Preclinical	IV safety and organ clearance
Borophene biosensor	Class II diagnostic device	Prototype	Stability and scale-up
h-BN BNCT carrier	Drug/device combination	Early preclinical	Boron delivery and persistence

10. Future Perspectives

The next stage of 2D material biomedicine should move beyond isolated proof-of-concept studies toward clinically meaningful validation. Standardized characterization must become routine, with every study reporting lateral size distribution, thickness, zeta potential, surface chemistry, endotoxin level, colloidal stability, and degradation profile. Clinically relevant matrices must replace ideal buffer systems in biosensing studies, with sensors tested in serum, plasma, saliva, sweat, urine, interstitial fluid, or whole blood depending on intended use. The transition from ideal-buffer to real-matrix validation is the single most important step separating academic proof-of-concept work from clinically actionable data, and requires substantial investment in clinical-sample handling infrastructure that academic laboratories have historically underdeveloped.

Long-term safety studies are essential. For implantable devices, chronic studies over months in large animals are needed. For injectable agents, pharmacokinetics, biodistribution, clearance, reproductive toxicity, and immunotoxicity must be evaluated. AI-assisted biosensing will become increasingly important, with machine learning helping to correct drift, interpret multiplexed signals, compensate for device variability, and improve diagnostic classification [11]. The integration of 2D material hardware with AI software represents a convergence of two rapidly maturing technologies: 2D materials provide the high-sensitivity transduction, while AI provides the calibration, noise rejection, and clinical-decision support needed to convert raw signals into actionable diagnostic information.

Biodegradable and transient 2D devices may offer a faster route to clinical acceptance because they reduce concerns about permanent foreign material retention. BP and biodegradable MXenes are especially promising in this area. Finally, composite architectures will likely dominate future translation: no single 2D material is ideal for all biomedical needs, and the strongest platforms will combine MXene for conductivity, BP for biodegradability, MoS₂ for semiconducting sensing, h-BN for insulation, and Xenes for specialized imaging or therapy [12]. Heteroatom-doped graphdiyne and related analogues represent an additional emerging class of 2D materials whose tunable electronic structures may eventually complement the current biomedical 2D toolkit, although their biomedical translation remains at a basic-research stage [89].

11. Conclusion

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3007-3197

Print ISSN

3007-3189

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Two-dimensional materials beyond graphene have evolved from laboratory curiosities into a diverse biomedical toolkit. TMDs provide powerful platforms for drug delivery, gene delivery, photothermal therapy, and multimodal cancer theranostics. MXenes combine conductivity, hydrophilicity, photothermal performance, antibacterial behavior, and neural interface capability. Black phosphorus offers a rare combination of optical activity, drug loading, and biodegradation into biologically useful phosphate species (HPO_4^{2-} and H_2PO_4^- at physiological pH). Xenes and h-BN expand the field into high-Z imaging, radiosensitization, borophene biosensing, BNCT, and implant coatings. Meanwhile, 2D material FET biosensors and wearable devices are pushing diagnostic sensitivity toward femtomolar, attomolar, and even lower concentration regimes.

The field is now entering a translational phase. The central challenge is no longer whether 2D materials can perform impressive biomedical functions; it is whether they can be made reproducibly, tested rigorously, manufactured safely, and approved through clear regulatory pathways. Among the platforms reviewed, three trajectories appear most proximate to clinical translation: MXene-coated flexible neural electrodes, which address the mechanical mismatch of conventional metal probes and have demonstrated superior electrophysiological performance in rodent chronic recordings; MoS_2 FET biosensors, which have achieved femtomolar-to-attomolar sensitivity for cancer, cardiac, and infectious disease biomarkers with clinical sample validation; and borophene lateral flow immunoassays, which offer a manufacturable near-term format for point-of-care protein detection [12]. The 5–10 year clinical translation window is, however, optimistic as it assumes successful resolution of the manufacturing, long-term safety, and regulatory barriers identified in Section 9, none of which is guaranteed. The next decade will determine whether 2D materials beyond graphene remain a promising laboratory platform or graduate into routine clinical tools for therapy, diagnostics, and continuous health monitoring.

Acknowledgements

The authors would like to thank their respective institutions for providing the necessary facilities and academic environment to carry out this research. No external assistance was received for this study.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contribution

Faizan Azmat contributed to the conceptualization of the study, research design, and overall supervision of the work. Safdar Abbas performed the literature review on biosensors and wearable platforms, data curation, coordination of the manuscript and figure preparation. Ali Murtaza contributed to the literature review on transition metal

Online ISSN

3007-3197

Print ISSN

3007-3189

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dichalcogenides and MXenes. Ali Shabaz contributed to the literature review on black phosphorus and Xenes, and table preparation. Samra Ashfaq contributed to the literature review on biocompatibility, toxicology, and clinical translation, writing assistance, and reference management. All authors reviewed and approved the final manuscript.

List of Abbreviations

2D: Two-dimensional; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ATP: Adenosine triphosphate; BCI: Brain-computer interface; BNCT: Boron neutron capture therapy; BP: Black phosphorus; BPA: Boronophenylalanine; BUN: Blood urea nitrogen; CGM: Continuous glucose monitoring; CT: Computed tomography; CTL: Cytotoxic T lymphocyte; CVD: Chemical vapour deposition; DAMP: Damage-associated molecular pattern; DC: Dendritic cell; DOX: Doxorubicin; ECoG: Electrocorticography; EMG: Electromyography; EPR: Enhanced permeability and retention; FET: Field-effect transistor; GMP: Good manufacturing practice; h-BN: Hexagonal boron nitride; HA: Hydroxyapatite; HF: Hydrofluoric acid; HMGB1: High-mobility group box-1 protein; hMSC: Human mesenchymal stem cell; HU: Hounsfield unit; ICD: Immunogenic cell death; ICP-MS: Inductively coupled plasma mass spectrometry; ISF: Interstitial fluid; LFA: Lateral flow immunoassay; LFP: Local field potential; LOD: Limit of detection; LPE: Liquid-phase exfoliation; MARD: Mean absolute relative difference; MAX: $M_{n+1}AX_n$ phase (M = early transition metal, A = A-group element, X = C or N); MIC: Minimum inhibitory concentration; MRI: Magnetic resonance imaging; MRSA: Methicillin-resistant *Staphylococcus aureus*; MXene: Two-dimensional transition metal carbide/nitride; NIR: Near-infrared; NMP: N-methyl-2-pyrrolidone; PA: Photoacoustic; PBS: Phosphate-buffered saline; PCE: Photothermal conversion efficiency; PDT: Photodynamic therapy; PEG: Polyethylene glycol; PEI: Polyethylenimine; PLGA: Poly(lactic-co-glycolic acid); PMA: Premarket approval; PSA: Prostate-specific antigen; PTT: Photothermal therapy; PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone; QD: Quantum dot; ROS: Reactive oxygen species; RUNX2: Runt-related transcription factor 2; SDT: Sonodynamic therapy; SNR: Signal-to-noise ratio; TMD: Transition metal dichalcogenide; TRL: Technology readiness level; UV-PIT: UV photoinduced immobilization technique; VEGF: Vascular endothelial growth factor; ZOI: Zone of inhibition.

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