



# Boron nitride nanomaterials for cancer therapy: Tailor-made strategies

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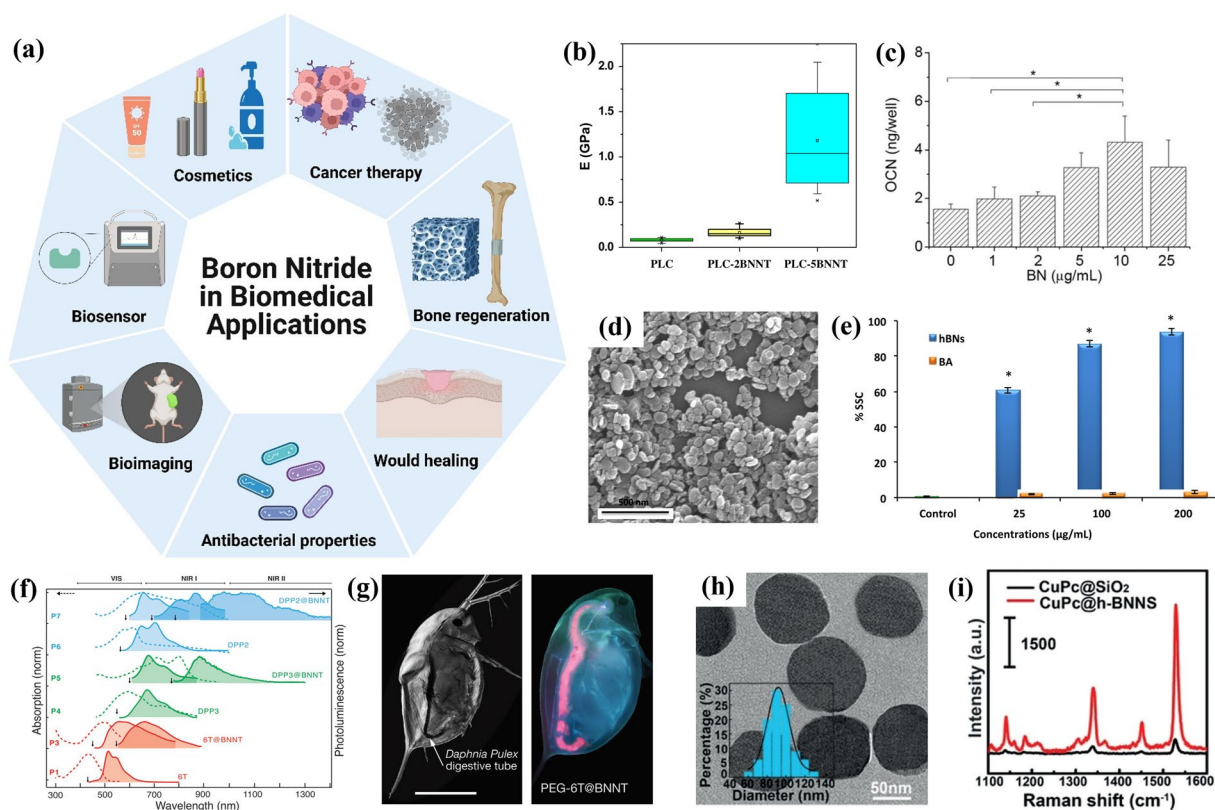
Boron nitride (BN) nanomaterials are an emerging biomaterial with great potential for cancer treatment owing to their excellent biocompatibility, light weight, high chemotherapeutic drug loading capacity (> 300 wt%), stimuli-responsive release behavior (such as pH and neutron irradiation), and unique biological activity. The objective of this review is to provide a comprehensive overview of the latest advancements in the field of tailoring BN nanomaterials for cancer therapy. The review will establish the design principles of BN nanomaterials that are suitable for cancer treatment. It will summarize the synthesis methods, the ways to improve their dispersibility in aqueous solution, and the biocompatibility and the biodegradability of BN nanomaterials. Furthermore, a comprehensive review of the application of BN nanomaterials in cancer therapy will be presented, encompassing the delivery of chemotherapy drug, their intrinsic anticancer effects, boron neutron capture therapy, cancer immunotherapy, irreversible electroporation, and combination therapy. BN nanomaterials with tunable sizes ranging from a few to hundreds of nanometers show great promise in the treatment of various cancers, such as prostate cancer, breast cancer, and glioblastoma. Finally, we will present prospects regarding future directions in this evolving field of tailoring BN nanomaterials to reshape cancer therapy.

## Introduction

Boron nitride (BN) is composed of alternatively arranged boron (B) and nitrogen (N) atoms, as a structural analog of carbon [1]. BN presents four distinct crystal forms, including sp<sup>2</sup>-hybridized hexagonal and rhombohedral phases, and sp<sup>3</sup>-hybridized cubic and wurtzite phases [2, 3]. Among them, hexagonal BN is the phase that is most thermodynamically stable and prevalent under normal conditions [3, 4]. A parallel can be drawn with graphite, as hexagonal BN exhibits high mechanical strength, excellent lubrication, and high thermal conductivity, a consequence of the presence of strong  $\sigma$  (sigma) bonds within the layers and weak van der Waals forces between the layers [2]. However, due to the nature of the heteroatom bonding and the electronegativity disparity between the B and N atoms, the B–N bond in BN is partially ionic, as opposed to the purely covalent C–C bond in graphite. The partial ionic feature of the B–N bonds impedes the electron delocalization in their  $\pi$  bonds, resulting in a wide

band gap (5.5~6.0 eV), electrical insulation, and a white/translucent appearance of BN materials [2]. In contrast, graphite has a narrow band gap (~0 eV), conductive properties, and a black appearance [2].

BN is an emerging material in the field of biomedical research due to its excellent biocompatibility, special chemical composition, distinctive physicochemical characteristics, and unique biological activities (Fig. 1). For instance, the United States Food and Drug Administration (FDA) has reported the extensive utilization of hexagonal BN particles in personal care products, including skincare, makeup (lipstick, foundation, blush, eye shadows), and hair care (shampoo and hair conditioner), owing to their exceptional lubricating properties and white/translucent appearance [5]. In the last decade, BN nanomaterials have garnered mounting interest in the field of cancer therapy, primarily due to their favorable biocompatibility, light weight, superior loading capacity, and distinctive bioactivity



**Figure 1:** (a) Application of BN materials in biomedical fields. Created in BioRender. Li, X. (2025) <https://BioRender.com/l26a081>. (b) BN nanotubes reinforce the elastic modulus of polylactide-polycaprolactone copolymer for bone regeneration. Reproduced with permission from Ref. 9, copyright 2010 Elsevier. (c) BN nanotubes enhance osteogenic differentiation of mesenchymal stem cells for bone regeneration. Reproduced with permission from Ref. 12, copyright 2016 John Wiley and Sons. Osteocalcin (OCN) is a late marker of osteogenic differentiation. (d-e) BN nanoparticles accelerate wound healing: SEM image of BN nanoparticles (d) and the side scatter (SSC) intensity of HUVEC cells exposed to BN or boric acid (BA) (e). Reproduced with permission from Ref. 16, copyright 2019 American Chemical Society. (f-g) Encapsulation of dyes inside BN nanotubes enhances photostability, shifts fluorescence to near infrared (f), and serves as nanoprobes for *in vivo* monitoring of *Daphnia Pulex* (g). Reproduced with permission from Ref. 17, copyright 2020 John Wiley and Sons. (h-i) BN nanosheets for real-time monitoring of microRNA by surface-enhanced Raman spectroscopy (SERS): TEM image of BN nanosheets (h) and the enhancement of SERS signal of copper(II) phthalocyanine (CuPc) by BN nanosheets (i). Reproduced with permission from Ref. 22, copyright 2019 John Wiley and Sons.

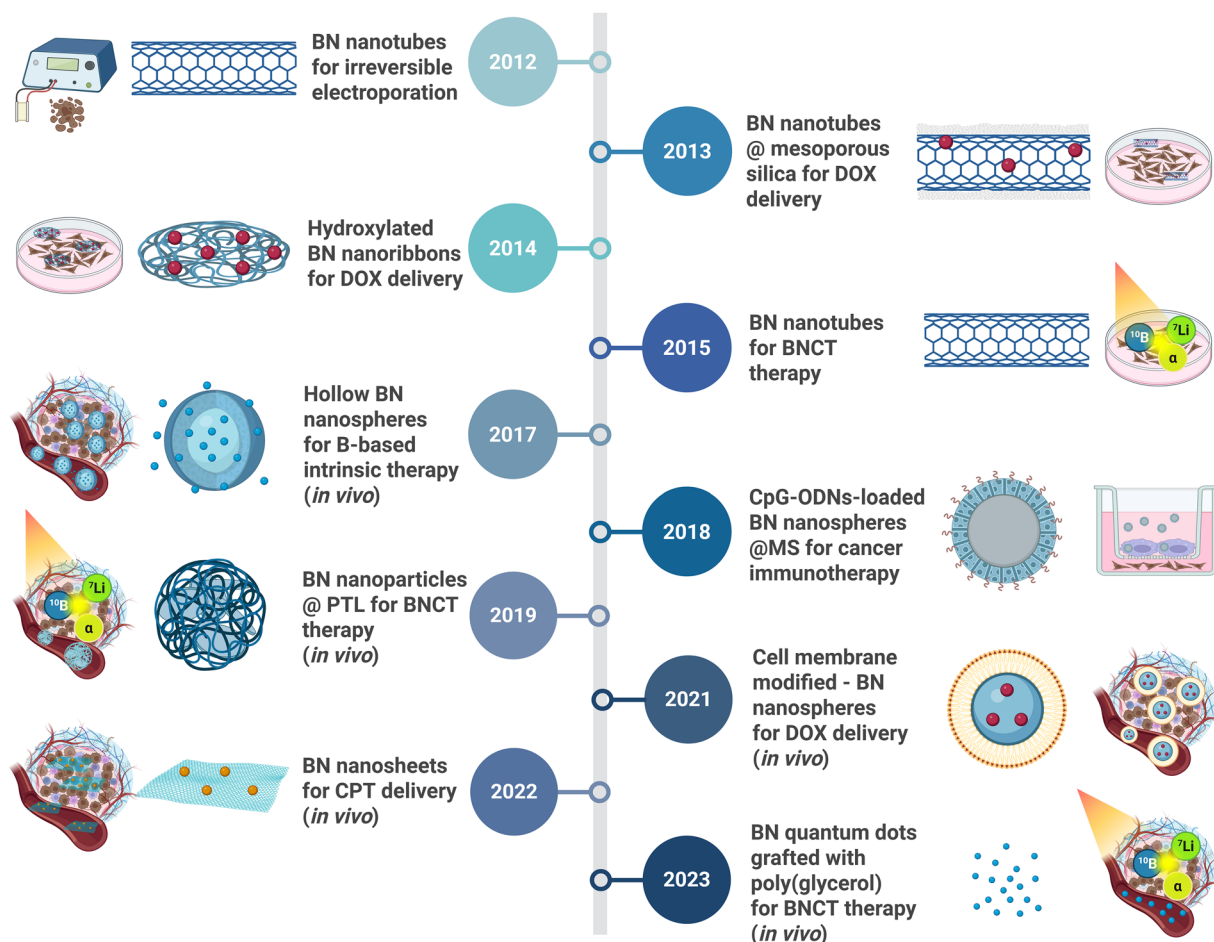
[6–8]. BN nanomaterials possess exceptional mechanical properties and the capacity to enhance osteogenic differentiation, thus indicating their potential for utilization in bone regeneration [9–12]. They also have antibacterial properties and promote wound healing [13–16]. In addition, BN nanomaterials are promising in bioimaging owing to their intrinsic fluorescence emission and their ability to encapsulate organic dye molecules to reduce the toxicity and increase the photostability [17, 18]. Finally, BN nanomaterial-based biosensors have been reported to detect molecules including, but not limited to, acetone, creatinine and cancer antigen [19–22].

This review will focus on tailoring BN nanomaterials for cancer therapy, presenting an up-to-date overview of their progress. The initial section will set out the design principles and synthesis methods of BN nanomaterials suitable for cancer treatment. The subsequent section will summarize the biocompatibility and biodegradability of BN nanomaterials. The

application of BN nanomaterials in cancer therapy will be comprehensively clarified, including chemotherapy drug delivery, intrinsic anticancer effects, boron neutron capture therapy, cancer immunotherapy, irreversible electroporation, and combination therapy (Fig. 2). Finally, we will highlight prospects, the emerging trends, and future directions in this developing field of BN nanomaterials' tailoring to reshape the cancer therapy.

## Synthesis of BN nanomaterials suitable for cancer therapy

Several review papers have hitherto been published concerning the synthesis, functionalization, structure, and properties of BN nanomaterials with different dimensions, including zero-dimensional (0D) BN nanoparticles and quantum dots, one-dimensional (1D) BN nanotubes and nanoribbons, and two-dimensional (2D) BN nanosheets [2, 30]. The requirements and



**Figure 2:** Timeline of application of BN materials with different morphologies in different modalities of cancer therapy [6–8, 23–29]. Created in BioRender. Li, X. (2025) <https://BioRender.com/l26a081>

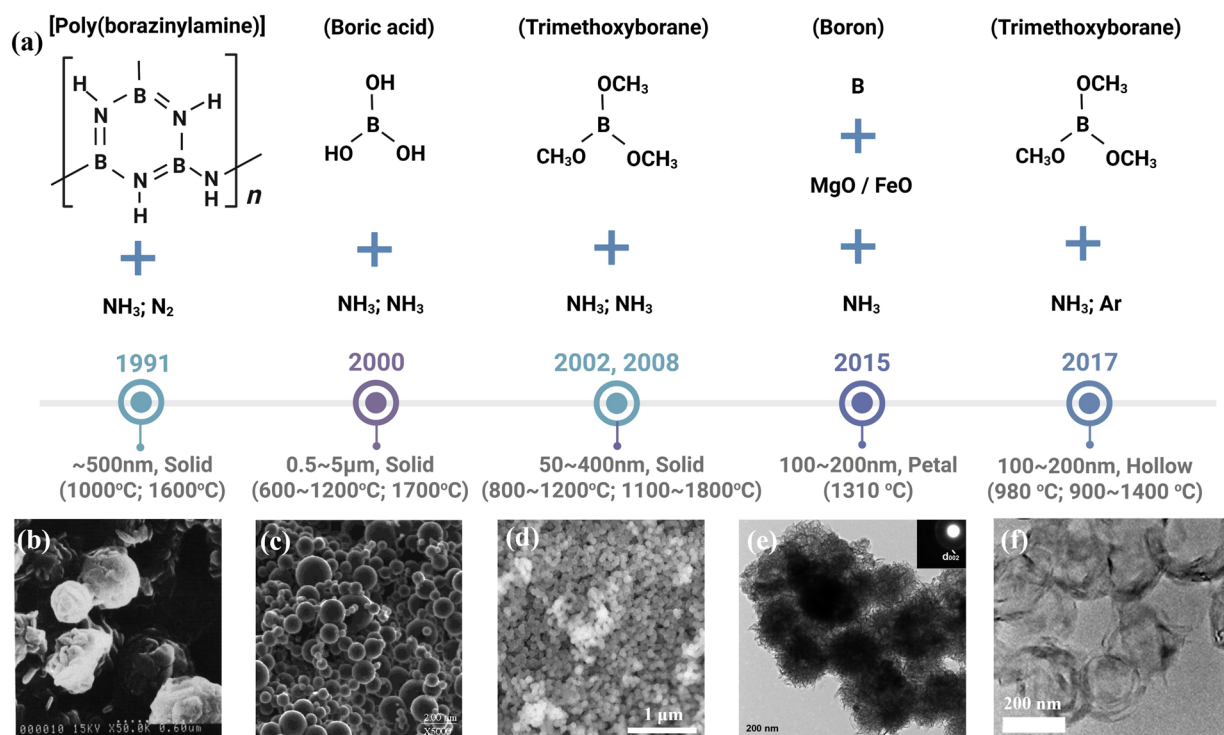
emphasis on BN nanomaterials are completely different when considering specific application scenarios. For example, for applications in mechanical and thermal conductivity enhancement, high synthesis temperature (e.g., chemical vapor deposition, 1100 ~ 1800 °C), high crystallinity, and few structural defects in BN materials are important. However, in the context of cancer therapy, BN nanomaterials should follow important design principles: easy dispersion in water, high biological activity, and easy degradation or excretion from the body. To achieve these goals, the following strategies can be considered: reducing the particle size, having a high number of active groups, such as -OH groups, increasing the specific surface area, lowering the synthesis temperature (e.g., chemical vapor deposition, 800 ~ 1050 °C), and reducing the degree of crystallinity.

### Synthesis routes of nanoscale BN materials

The synthesis of BN nanomaterials for cancer therapy can be categorized into two distinct approaches: bottom-up and

top-down. Bottom-up synthetic approaches refer to the construction of desired BN nanostructures through the assembly of boron and nitrogen-containing atoms or molecules, employing techniques such as chemical vapor deposition, hydrothermal/solvothermal methods, and pyrolysis reaction [2, 30]. Conversely, top-down synthetic approaches involve breaking down large BN bulk materials into desired nanoscale size through mechanical exfoliation techniques (such as ball milling and sonication), chemical exfoliation or assisted exfoliation [2, 30].

The typical preparation of 0D BN nanoparticles involves the use of chemical vapor deposition, with boron sources such as poly(borazinylamine), boric acid, trimethoxyborane, and boron, and nitrogen sources, including NH<sub>3</sub>, employed in the process (Fig. 3) [7, 31–35, 41, 42]. The synthesis of 0D BN quantum dots is typically accomplished through the utilization of hydrothermal or solvothermal methodologies (Fig. 4) [36–40]. The boron sources employed in these processes encompass boric acid and ammonia borane, while the nitrogen sources may include



**Figure 3:** (a) Timeline of BN nanoparticle synthesis by chemical vapor deposition [7, 31–35]. Created in BioRender. Li, X. (2025) <https://BioRender.com/I26a081>. (b) SEM image of BN particles using poly(borazinyllamine) precursor synthesized at 1000 °C followed by treatment at 1600 °C. Reproduced with permission from Ref. 31, copyright 1991 John Wiley and Sons. (c) SEM image of BN particles using boric acid precursor synthesized at 1000 °C followed by treatment at 1700 °C under  $\text{NH}_3$  atmosphere. Reproduced with permission from Ref. 32, copyright 2000 American Chemical Society. (d) SEM image of BN nanoparticles using trimethoxyborane precursor synthesized at 980 °C followed by treatment at 1400 °C under  $\text{NH}_3$  atmosphere. Reproduced with permission from Ref. 34, copyright 2008 John Wiley and Sons. (e) TEM image of BN nanoparticles using boron precursor synthesized at 1310 °C. Reproduced with permission from Ref. 35, copyright 2005 American Chemical Society. (f) TEM image of BN nanoparticles using trimethoxyborane precursor synthesized at 980 °C followed by treatment at 1400 °C in Ar atmosphere. Reproduced with permission from Ref. 7, copyright 2017, the Authors, Published by Nature Portfolio.

ammonia solution, melamine, urea, aliphatic amine, and ammonia borane [36–40].

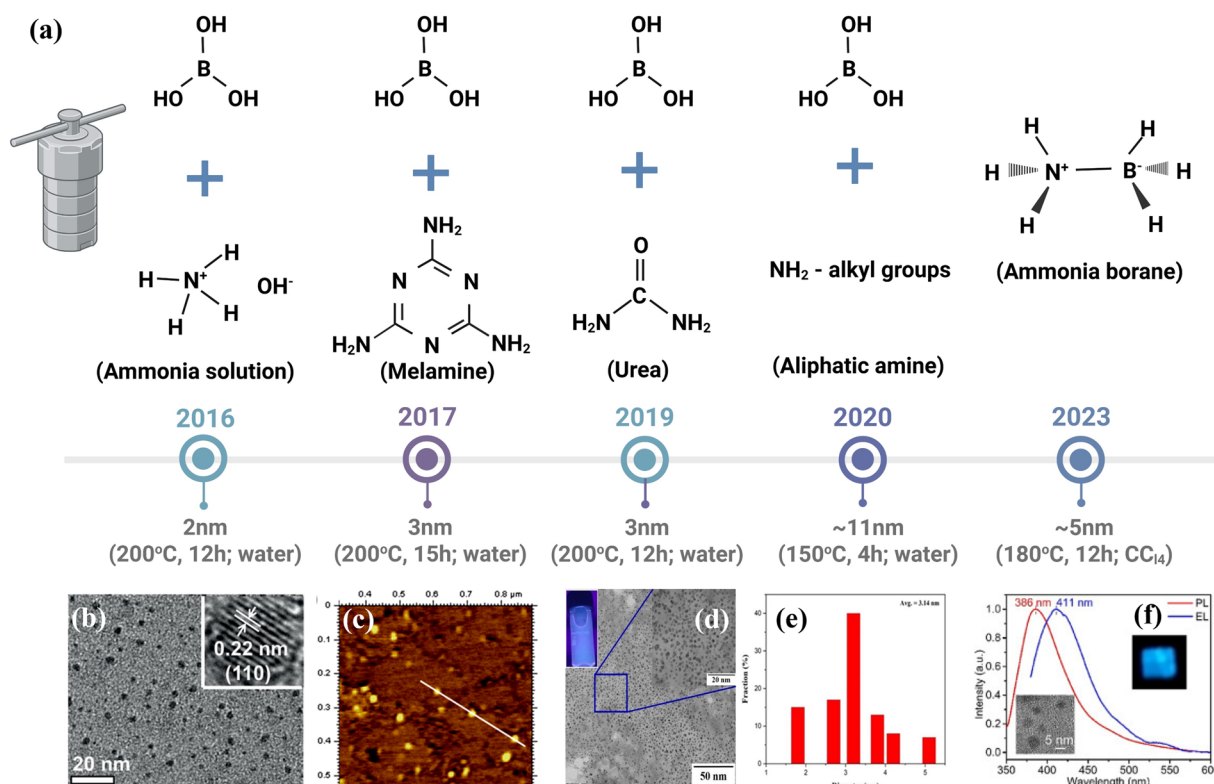
For the synthesis of 0D BN nanoparticles, the chemical vapor deposition method was mostly used in the early stage. By adjusting the synthesis parameters such as the type of boron sources, synthesis temperature, post-treatment temperature/atmosphere, it is possible to tune the particle size, uniformity, crystallinity, and so on. For example, the use of trimethoxyborane or boron as a precursor is more promising than other precursors for obtaining uniform BN nanoparticles. Post-treatment in an Ar atmosphere tends to produce a hollow structure, while post-treatment in an ammonia and nitrogen atmosphere generally produces solid particles. In addition, the crystallinity of synthesized BN nanoparticles is closely related to the synthesis and post-treatment temperature. The higher the synthesis and post-treatment temperature, the higher the crystallinity. However, according to existing reports, it is difficult to prepare nanoparticles below 50 nm by the chemical vapor deposition method. In order to prepare BN quantum dots with smaller particle sizes, hydrothermal/solvothermal methods have attracted great attention in recent years.

The first synthesis of 1D BN nanotubes was achieved through the arc discharge method in 1995, followed by the thermal annealing method in 1999 [43, 44]. The synthesis of high-quality BN nanotubes was subsequently realized by chemical vapor deposition using boron powder as the boron source and MgO as the catalyst in 2002 [45]. The preparation of 2D BN nanosheets can be achieved through a variety of methods, including exfoliation techniques, pyrolysis reactions, and chemical vapor deposition [2, 30, 46].

### How to prepare highly dispersible BN nanomaterials in aqueous solution?

Pristine BN materials synthesized at high temperature are highly hydrophobic in nature. Both post-modification techniques and direct synthesis routes at moderate temperature are effective in the preparation of BN nanomaterials that are easily dispersed in aqueous solution. In the early stages of BN nanomaterial synthesis for biomedical application, post-modification routes have frequently been used to enhance their dispersibility through





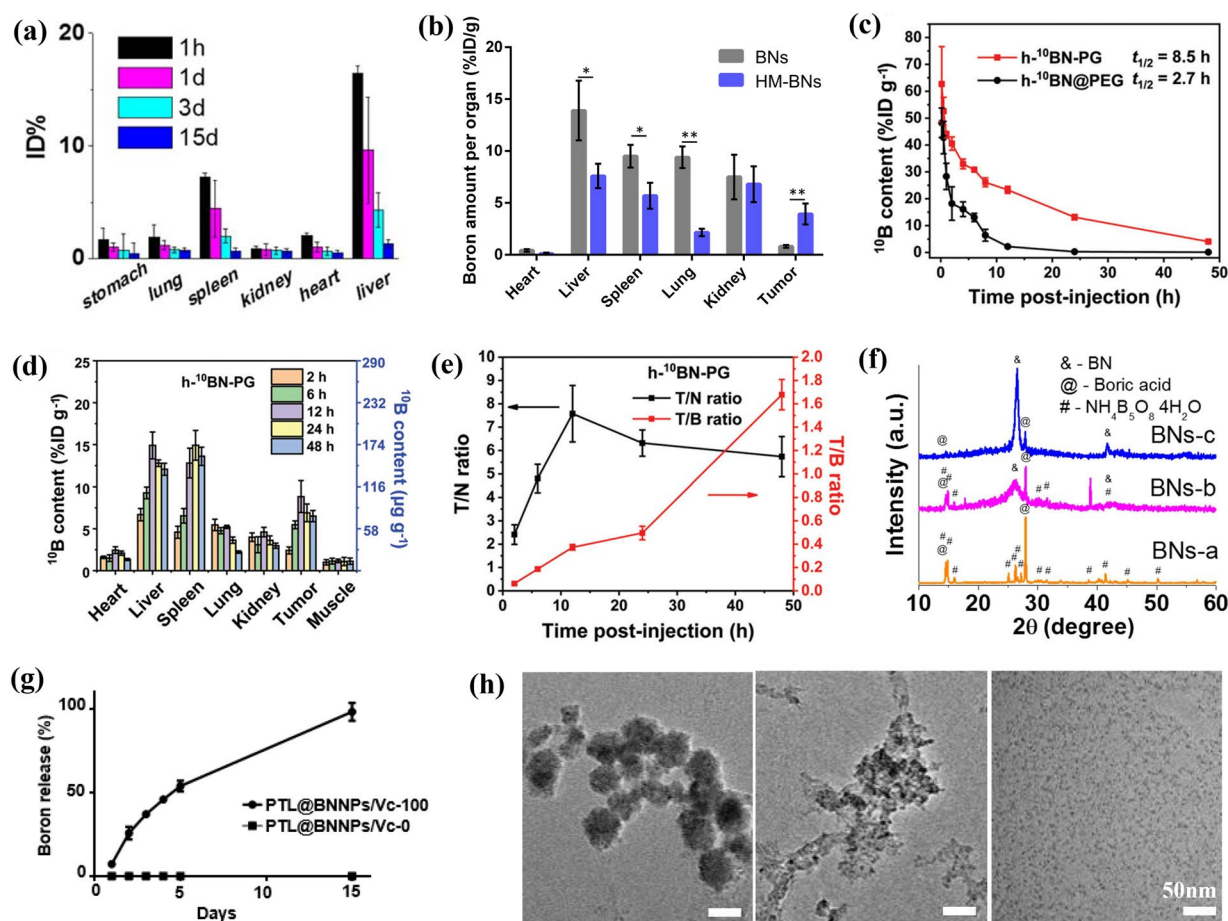
**Figure 4:** (a) Timeline of BN quantum dot synthesis using hydrothermal/solvothermal methods [36–40]. Created in BioRender. Li, X. (2025) <https://BioRender.com/l26a081>. (b) TEM image of BN quantum dots synthesized using boric acid and ammonia solution. Reproduced with permission from Ref. 36, copyright 2016 John Wiley and Sons. (c) AFM image of BN quantum dots synthesized using boric acid and melamine. Reproduced with permission from Ref. 37, copyright 2017 American Chemical Society. (d-e) TEM image and particle size distribution of TEM image of BN quantum dots synthesized using boric acid and urea. Reproduced with permission from Ref. 38, copyright 2019, the Authors, Published by IOP. (f) Photoluminescence and TEM image of BN quantum dots synthesized using ammonia borane. Reproduced with permission from Ref. 40, copyright 2023 Elsevier.

weak interactions or covalent bonding. For example, BN nanotubes have been reported to be modified with synthetic polymers, peptides, nucleotides, and polysaccharides through weak interactions, such as  $\pi$  stacking interaction, electrostatic interactions, and nonspecific interactions [47–52]. For example, B sites in BN nanotubes can be activated to become covalently bonded to hydroxyl groups when oxidized in an air atmosphere followed by sonication in water or hydroxyl radical ( $\bullet$ OH) -generating reagents, such as hydrogen peroxide H<sub>2</sub>O<sub>2</sub> [53, 54]. Later, some reports on the direct synthesis of highly water-dispersible BN nanomaterials gradually emerged [6, 7]. For example, hydroxyl-abundant B precursor (boric acid) was used to substitute the carbon (C) component in graphitic carbon nitride (g-C<sub>3</sub>N<sub>4</sub>) powders at moderate temperature (800 °C) to synthesize BN nanoribbons with extremely high numbers of hydroxyl groups and superior dispersibility ability in aqueous solution up to 2 mg mL<sup>-1</sup> [6].

### In vivo biocompatibility of BN nanomaterials

It is generally considered that the BN materials themselves are non-toxic and possess excellent biocompatibility. In 2012, Ciofani

et al. first carried out *in vivo* biocompatibility evaluation of BN nanotubes coated with G-chitosan by administering them intravenously into rabbits at a dose of 1 mg/kg, and the analysis of the hematological and blood chemistry parameters up to 3 days suggested no apparent toxicity on blood, liver, and kidney functions [55]. In 2015, Ciofani et al. reported on the *in vivo* biocompatibility of BN nanotubes coated with gum Arabic in planarians at doses of 100 or 200  $\mu$ g/g, suggesting no significant adverse effects on stem cell biology and tissue regeneration [56]. However, there is a degree of concern regarding the potential effects of high aspect ratio BN nanotubes on pulmonary function, owing to their one-dimensional configuration. In 2023, Luna et al. reported the effects of BN nanosheets and BN nanotubes on the lungs of mice by means of single oropharyngeal aspiration, suggesting that low aspect ratio BN nanosheets are safer than high aspect ratio BN nanotubes [57]. BN nanosheets were rapidly cleared from the lungs and did not induce pulmonary fibrosis, whereas high aspect ratio BN nanotubes were poorly cleared from the lungs and induced chronic inflammation and fibrosis [57].



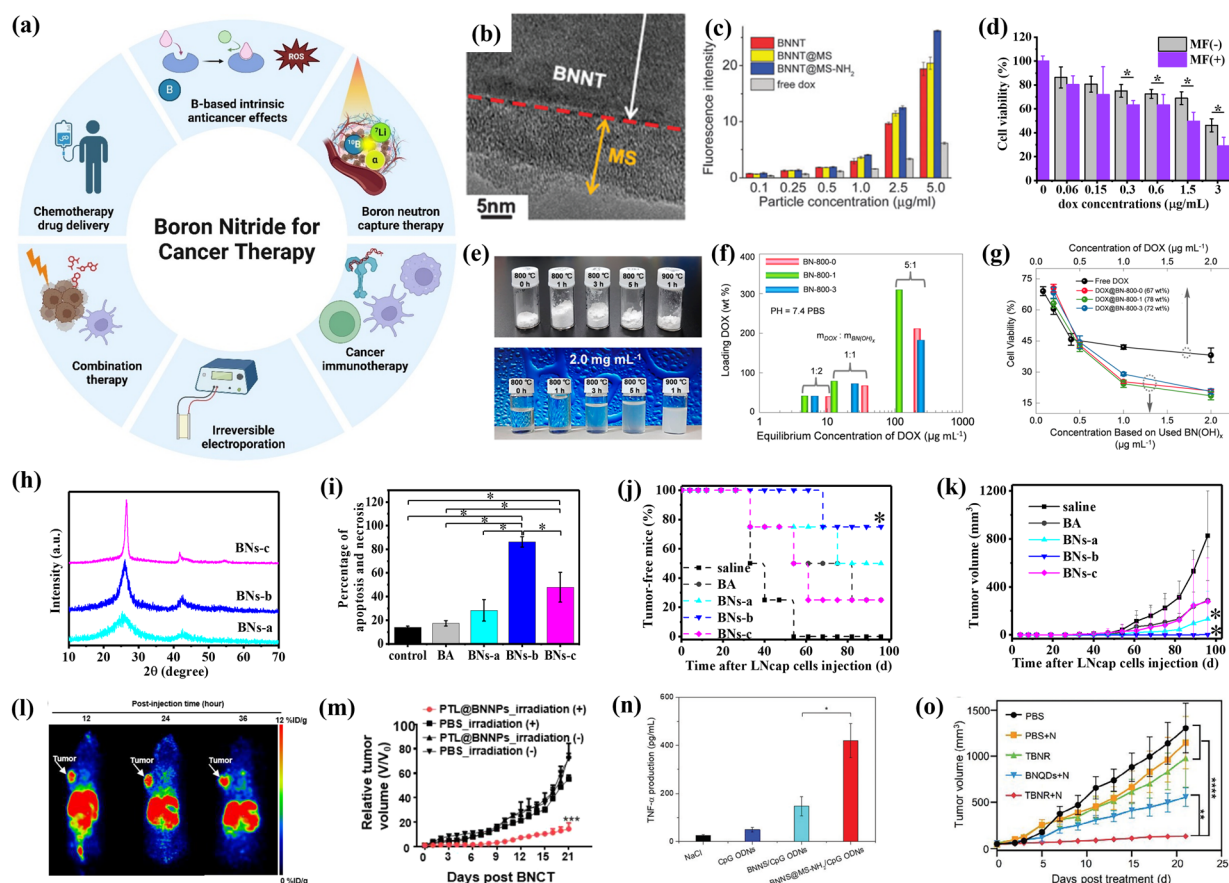
**Figure 5:** (a) Biodistribution of BN nanospheres after intravenous administration. Reproduced with permission from Ref. 7, copyright 2017, the Authors, Published by Nature Portfolio. (b) Biodistribution of BN nanospheres before (BNs) and coated with cancer cell membrane (HM-BNs) after intravenous injection into HeLa tumor-bearing BALB/c nude mice. Reproduced with permission from Ref. 28, copyright 2021, the Authors, Published by Dovepress. (c-e) Pharmacokinetics of BN nanoparticles in CT26 tumor-bearing mice after intravenous injection: Blood circulation profiles of BN nanoparticles with different surface modification (c); Time course of biodistribution (d); Time course of tumor-to-normal tissue (T/N) and tumor-to-blood (T/B) ratios (e). Reproduced with permission from Ref. 8, copyright 2023 John Wiley and Sons. (f) Degradation of BN nanospheres in aqueous solution for 3 days. Reproduced with permission from Ref. 7, copyright 2017, the Authors, Published by Nature Portfolio. (g-h) Cumulative boron release (g) and biodegradation (h) of BN nanoparticles coated with phase-transition lysozyme (PTL@BNNPs) in response to vitamin C. Reproduced with permission from Ref. 27, copyright 2019 American Chemical Society.

## Pharmacokinetics and biodegradability of BN nanomaterials

Pharmacokinetics, organ distribution, and clearance profiles of BN nanomaterials *in vivo* highly depend on their particle size and surface modification (Fig. 5). For example, after intravenous injection into healthy C57/BL6 mice, hollow BN nanospheres around 200 nm mainly accumulate in the reticuloendothelial system such as the liver and spleen, and the amounts in the different organs and tissues decrease with time owing to gradual degradation and clearance ranging from 1 h to 15 days [Fig. 5(a)] [7]. For example, after intravenous injection into HeLa tumor-bearing BALB/c nude mice, BN nanospheres around 100 nm are mainly found in the liver, spleen, and lungs, and BN nanospheres coated with cancer cell membrane (HM-BNs) show much higher accumulation at tumor sites and much

lower accumulation in the lungs than the pristine BNs due to the homotypic tumor targeting [Fig. 5(b)] [28]. <sup>10</sup>B-enriched BN nanoparticles around 8 nm grafted with poly(glycerol) (h-<sup>10</sup>BN-PG) demonstrate a prolonged blood circulation time than those grafted with poly(ethylene glycol) [Fig. 5(c)]. Moreover, h-<sup>10</sup>BN-PG nanoparticles show the highest accumulation at tumor sites and the highest tumor-to-normal tissue (T/N) ratio at 12 h after injection [Fig. 5(d-e)] [8].

The biodegradability of BN nanomaterials is contingent upon the crystallinity, the precursors, and the temperature at which they are synthesized [7, 58, 59]. BN nanomaterials with high crystallinity synthesized at high temperature are resistant to degradation under physiological conditions. Conversely, BN nanomaterials with low crystallinity synthesized at modest temperature can gradually degrade into boric acid and



**Figure 6:** (a) Application of BN materials in cancer therapy. Created in BioRender. Li, X. (2025) <https://BioRender.com/126a081>. (b–c) BN nanotubes for chemotherapy drug delivery: SEM image of BN nanotubes modified with mesoporous silica (b); Intracellular uptake of DOX for prostate cancer cells for DOX-loaded BN nanotube and those modified with mesoporous silica in contrast to free DOX (c). Reproduced with permission from Ref. 24, copyright 2013 Royal Society of Chemistry. (d) BN nanotubes modified with NaGdF<sub>4</sub>:Eu for targeted delivery of chemotherapy drug in the presence of a magnetic field. Reproduced with permission from Ref. 61, copyright 2014 Royal Society of Chemistry. (e–g) Highly hydroxylated BN nanoribbons with perfect suspension ability in aqueous solution up to 2 mg mL<sup>-1</sup> (e), unprecedented high loading capacity for DOX (f), and an excellent ability to enhance the anticancer effect of DOX drug (g). Reproduced with permission from Ref. 6, copyright 2014 American Chemical Society. (h–k) Intrinsic anticancer effects of hollow BN nanospheres in the treatment of prostate cancer: XRD patterns of BN nanospheres (h); The induction of cancer cell death by BN nanospheres (i); Percentage of tumor-free mice (j) and tumor volume (k) for control group, boric acid (BA) group and BN groups. Reproduced with permission from Ref. 7, copyright 2017, the Authors, Published by Nature Portfolio. (l–m) BN nanoparticles for BNCT therapy: Representative PET imaging of 4T1 tumor-bearing mice post intravenous injection of [<sup>64</sup>Cu]PTL@BNNPs (l); Tumor growth curves (m). Reproduced with permission from Ref. 27, copyright 2019 American Chemical Society. (n) BN nanospheres for cancer immunotherapy: *in vivo* immunostimulatory activity of CpG ODNs, BNNS/CpG ODNs, and BNNS@MS-NH<sub>2</sub>/CpG ODN complexes. Reproduced with permission from Ref. 26, copyright 2018 Royal Society of Chemistry. (o) BN quantum dots (BNQDs) for BNCT—chemodynamic (CDT) combination therapy: Tumor volumes of mice treated with PBS (control group), PBS + N (neutron irradiation), TBNR (Fe<sup>3+</sup>-BNQDs assembly), BNQDs + N and TBNR + N. Reproduced with permission from Ref. 62, copyright 2025 John Wiley and Sons.

ammonium borate hydrates [Fig. 5(f)] [7, 59]. Boron oxynitride nanomaterials with low crystallinity almost completely degraded within 7 days [60]. The coating of BN nanoparticles around 50 nm with a phase-transitioned lysosome (PTL) has been demonstrated to enable the on-demand degradation and rapid clearance of BN from the body via intravenous injection of vitamin C [Fig. 5(g–h)] [27].

## Applications of BN nanomaterials in cancer therapy

This review will comprehensively summarize research reports on the application of BN nanomaterials in cancer treatment, including chemotherapy drug delivery, intrinsic anticancer effects, boron neutron capture therapy, cancer immunotherapy, irreversible electroporation, and combination therapy (Fig. 6 and Table L).

TABLE 1: Boron nitrides for cancer therapy.

Modality	Morphology/Modification	Average size	Cargos and loading capacity	Evaluation models	Features	References
Chemotherapy drug delivery	BN nanotubes modified with mesoporous silica	Diameter: 50 ~ 80 nm; length: 1 $\mu$ m;	DOX; ~ 60 wt%	<i>In vitro</i> , LNCaP prostate cancer cells	Improving the suspension ability in aqueous solution and enhancing the intracellular delivery of DOX	24
Chemotherapy drug delivery	BN nanotubes modified with NaGdF <sub>4</sub> :Eu	Diameter: 50 ~ 80 nm; length: 1 $\mu$ m;	DOX; ~ 30 wt%	<i>In vitro</i> , LNCaP prostate cancer cells	Increasing cellular uptake and chemotherapy efficacy in the presence of an external magnetic field	61
Chemotherapy drug delivery	BN nanoribbons	A few to dozens of nanometers	DOX; > 300 wt%	<i>In vitro</i> , LNCaP prostate cancer cells	Perfect suspension ability up to 2 mg mL <sup>-1</sup> ; pH-dependent release of DOX; Enhancing the anticancer effect of DOX	6
Chemotherapy drug delivery	BN nanospheres with a petal-like surface and porous structure	Diameter: 100 ~ 200 nm;	DOX; 0.055 mg/mg carriers	<i>In vitro</i> , IAR-6-1 neoplastic cells	Increasing the intracellular delivery of DOX	35
Chemotherapy drug delivery	BN nanospheres conjugated with folate	Diameter: 150 nm;	DOX; ~ 0.021 mg/mg carriers	<i>In vitro</i> , HeLa cervical cancer cells	Exhibiting a much higher toxicity to HeLa cells with high expression of folate receptors	63
Chemotherapy drug delivery	BN nanotubes coated with GBM cell membrane	Hydro-dynamic diameter: 300 nm;	DOX; 2.15 wt%	<i>In vitro</i> , glioblastoma cells	Homotypic targeting and drug delivery in glioblastoma cells	64
Chemotherapy drug delivery	BN nanosphere coated with HeLa cell membrane	Diameter: 100 nm;	DOX; ~ 0.862 mg/mg carriers	<i>In vitro/in vivo</i> , HeLa cervical cancer cells	Tumor-targeted delivery of DOX; Exhibiting a much higher tumor inhibition effect <i>in vivo</i>	28
Chemotherapy drug delivery	Highly hydroxylated BN nanosheets	Diameter: 47 nm;	CPT; ~ 170 wt%	<i>In vitro/in vivo</i> , 4T1 breast cancer cells	Enhancing the anticancer effects of poorly water-soluble CPT drug	29
Intrinsic anticancer effects	Hollow BN nanospheres	Diameter: 200 nm; Wall thickness: 50 ~ 60 nm or 20 nm	–	<i>In vitro/in vivo</i> , LNCaP and DU-145 prostate cancer cells	Inducing apoptosis in prostate cancer cells; Inhibiting tumor growth in subcutaneous and orthotopic LNCaP-bearing mouse models	7
Intrinsic anticancer effects	BN nanoparticles with platelet-like structure	Lateral size dimension: 50 nm	–	<i>In vitro</i> , DU-145 prostate cancer cells	Increasing apoptosis in DU-145 cells by inducing mitochondrial dysfunction and ROS generation	65
Intrinsic anticancer effects	Boron oxynitride nanospheres	Diameter: 100 ~ 500 nm	–	<i>In vitro/in vivo</i> , 4T1 breast cancer cells	Enzyme-like activities; Inhibiting tumor growth by 97% in 4T1-bearing mouse models	60
BNCT	BN nanotubes	–	–	<i>In vitro</i> , B16 melanoma cells	Three times more accumulation in B16 melanoma cells than clinically used BSH	25



TABLE 1: (continued)

Modality	Morphology/Modification	Average size	Cargos and loading capacity	Evaluation models	Features	References
BNCT	BN nanoparticles coated with PTL	Diameter: 50 nm	–	<i>In vitro/in vivo</i> , 4T1 breast cancer cells	On-demand degradation of BN nanoparticles; suppressing tumor growth with negligible side effect	27
BNCT	<sup>10</sup> B-enriched BN nanoparticles grafted with poly(glycerol)	Diameter: 8 nm	–	<i>In vitro/in vivo</i> , CT26 colon cancer cells	Almost completely eradicating the tumors in CT26-bearing mouse models	8
Immunotherapy	BN nanospheres modified with mesoporous silica	Diameter: 100 nm	CpG-ODNs	<i>In vitro</i> , 4T1 breast cancer cells and RAW264.7 macrophages	Enhancing the delivery of CpG-ODNs into macrophages, triggering immune response, and inhibiting cancer cell growth	26
Irreversible electroporation	BN nanotubes	Diameter: 1 ~ 3 nm; length: < 2 μm;	–	<i>In vitro</i> , HeLa cervical cancer cells	Local amplification of electric field and 2.2-fold reduction in cancer cell viability in the presence of BN nanotubes	23
Combination therapy	BN particles	–	IGG and DOX	<i>In vitro</i>	Combination of photothermal therapy with chemotherapy	66
Combination therapy	<sup>10</sup> B-enriched BN nanosheets	Size: 50 ~ 100 nm; Thickness: 3.5 nm	DOX	<i>In vitro/in vivo</i> , triple-negative breast cancer cells	Combination of BNCT with chemotherapy to generate synergistic effects; neutron irradiation-triggered DOX release; enhancing antitumor efficacy	67
Combination therapy	<sup>10</sup> B-enriched BN nanostructures	–	TLR agonist R837	<i>In vitro/in vivo</i> , 4T1 breast cancer cells	Combination of BNCT with cancer immunotherapy to generate synergistic effects; inhibiting distal tumor growth; and preventing metastasis	68
Combination therapy	BN nanoflakes coated with cancer cell membrane	Hydro-dynamic size: 300 ~ 400 nm;	DOX; ~ 0.023 mg/mg	<i>In vitro</i> , glioblastoma multiforme cells (U87-MG) and microglia (HMC3)	Combination of chemotherapy with M2 microglia polarization	69
Combination therapy	BN nanoparticles modified with cancer cell membrane and acylated TAT peptides	Diameter: 100 nm	IGG and DOX; 360% and 280%	<i>In vitro/in vivo</i> , HepG2 liver cancer cells	Combination of photothermal therapy with chemotherapy to generate synergistic effects; suppressing tumor growth	70
Combination therapy	<sup>10</sup> B-enriched BN quantum dots with Fe <sup>3+</sup>	Size-switchable: 3 nm, 65 nm	–	<i>In vitro/in vivo</i> , 4T1 breast cancer cells	Combination of BNCT with CDT to generate synergistic effects; inducing immunogenic cell death; and suppressing tumor growth	62

## Chemotherapy drug delivery

The mode of action of a chemotherapy drug is primarily the interference of DNA synthesis and mitosis, resulting in the death of rapidly growing and dividing cells, such as cancer cells. However, the utilization of chemotherapy drugs is accompanied by several disadvantages, including the nonspecific damage to some rapidly differentiating healthy cells, poor bioavailability, the requirement of high doses, severe undesirable side effects, and the development of multiple drug resistance [71]. The objective of chemotherapy drug delivery system is to address these issues by facilitating the delivery of drugs to the desired sites of therapeutic action through passive or active targeting, thereby enhancing the bioavailability of drugs and reducing adverse side effects [71]. Over the past decades, versatile delivery materials have been developed, including lipids, polymers, and inorganic carriers. Boron nitride nanomaterials are promising chemotherapy drug delivery systems due to their excellent biocompatibility, light weight, high loading capacity, and tunable morphology [6, 24, 61].

Doxorubicin (DOX) is a widely used chemotherapy drug to treat many different types of cancer. Boron nitride nanomaterials with different morphologies, structures, and hydroxylation degrees, including nanotubes, nanospheres, and nanoribbons, have been used to deliver DOX chemotherapy drug. In 2013, we reported that the shorten BN nanotubes enabled a high DOX loading capacity of approximately 60 wt % and improved the intracellular delivery of DOX into prostate cancer cells by approximately three times compared to free DOX [24]. Moreover, the surface modification of shorten BN nanotubes with mesoporous silica, especially one grafted with amino groups, can improve their suspension capacity in aqueous solutions and further enhance the intracellular delivery of DOX [24]. In 2014, we reported the surface modification of shorten BN nanotubes with NaGdF<sub>4</sub>:Eu, which imparts both fluorescence imaging to track them and magnetic targeting properties to enhance the intracellular delivery of DOX into cancer cells *in vitro* using an external magnetic field [61]. In 2014, we reported the one-pot synthesis of highly hydroxylated boron nitride nanoribbons with perfect suspension ability in aqueous solution up to 2 mg mL<sup>-1</sup> [6]. The unprecedented high loading capacity for DOX of about 300 wt% due to the  $\pi$ - $\pi$  stacking interactions between the conjugated BN domain and drug molecules was found, and pH-dependent release of the drug payloads and the excellent ability to enhance the anticancer effect of DOX drug *in vitro* were established [6]. In 2015, Sukhorukova et al. reported the synthesis of BN nanospheres with a petal-like surface and porous structure for the intracellular delivery of DOX into IAR-6-1 neoplastic cells [35]. In 2016, Feng et al. reported the folate conjugation of BN nanospheres for the intracellular delivery

of DOX drug into HeLa cells with high expression of folate receptors, which showed a much higher cytotoxicity than free DOX and BN/DOX without folate conjugation *in vitro* [63]. In 2021, Feng et al. further reported the encapsulation of BN nanospheres with cell membrane derived from HeLa cells for tumor-targeted delivery of DOX drug, which exhibited a much higher tumor inhibition effects *in vivo* than free DOX and BN/DOX without cell membrane [28].

In 2022, Weng et al. reported the synthesis of highly hydroxylated BN nanosheets with excellent suspension ability in aqueous solution of 1 mg mL<sup>-1</sup>, which could load about 170 wt % of camptothecin (CPT), a kind of poorly water-soluble anticancer drug, and enhance the anticancer effects of CPT drug *in vitro* and *in vivo* [29].

## Intrinsic anticancer effects

Epidemiological studies suggest that high dietary boron (B) intake may reduce the risk of cancer, including prostate, cervical, and lung cancer [72–74]. B-containing compounds inhibited some enzymatic activities, such as serine protease and nicotinamide adenine dinucleotide (NAD)-dehydrogenase, reduced intracellular calcium signaling and storage, and regulated reactive oxygen species (ROS) levels, which accounted for their effects on inhibiting cancer cell proliferation and inducing apoptosis of cancer cells [75, 76]. Therefore, B-containing compounds have been developed as cancer preventive and therapeutic agents [77]. For example, Bortezomib was approved by FDA as the first B-containing anticancer drug for the treatment of multiple myeloma and mantle cell lymphoma in 2003 based on its proteasome inhibiting properties.

However, because soluble B compounds were associated with short half-life periods, low bioavailability, and limited efficacy, BN nanoparticles were developed as an alternative formulation. In 2017, we reported hollow BN nanospheres with controlled crystallinity and boron release behavior for prostate cancer treatment [7]. Compared with soluble boric acid, the optimized BN nanospheres enhanced the caspase-3/7 activity, effectively induced the apoptosis in both LNCaP and DU-145 prostate cancer cells, and significantly inhibited tumor growth in both subcutaneous and orthotopic prostate tumor-bearing mouse models *in vivo* [7]. In 2020, Çulha et al. reported that BN nanoparticles increased the apoptosis rate in DU-145 prostate cancer cells by inducing mitochondrial dysfunction and ROS generation [65]. In 2021, Weng et al. reported boron oxynitride nanospheres with enzyme-like activities that catalyzed hydrogen peroxide H<sub>2</sub>O<sub>2</sub> to generate hydroxyl radicals, reduced cell viability by inducing apoptosis in 4T1 breast cancer cells *in vitro*, and inhibited tumor growth by 97% in breast tumor-bearing mouse models [60].

## Boron neutron capture therapy (BNCT)

BNCT is a targeted radiotherapy for cancer treatment, in which boron-10 ( $^{10}\text{B}$ )-containing compounds are administered to patients and accumulate at tumor sites, and upon irradiation with low-energy thermal neutrons, alpha ( $\alpha$ )-particles and lithium-7 ( $^7\text{Li}$ ) nuclei with high linear energy transfer are produced to selectively destroy cancer cells over short distances of about 9  $\mu\text{m}$ , close to the cell diameter. Two  $^{10}\text{B}$ -containing compounds, including boronophenylalanine (BPA) and mercaptoundecahydrododecaborane (BSH), have been used in the clinic for BNCT. Nanoparticles containing  $^{10}\text{B}$ , especially boron nitride nanoparticles with high boron content, are expected to deliver  $^{10}\text{B}$  more effectively to tumor sites, enhance the accumulation of  $^{10}\text{B}$  in tumors, and increase the ratios of tumor to normal tissue and tumor to blood [8, 25, 27].

In 2015, Nakamura et al. reported that BN nanotubes suspended in aqueous solution using DSPE-PEG2000 accumulated three times more than clinically used BSH when cocultured with B16 melanoma cells and exhibited much higher antitumor effects in BNCT treatment *in vitro* [25]. In 2019, Li et al. reported BN nanoparticles coated with a phase-transition lysozyme (PTL) for the BNCT treatment of triple-negative breast cancer and showed high tumor/blood, tumor/muscle, and tumor/fat ratios of approximately 2.7, 8.3, and 6.0, respectively, in 4T1 breast cancer-bearing mouse models [27]. Moreover, the coated BN nanoparticles exhibited on-demand degradation properties and were rapidly cleared from the major organs of the mice such as liver and spleen when vitamin C was injected intravenously after neutron irradiation to detach PTL protective coating [27]. In 2023, Zhang et al. reported that  $^{10}\text{B}$ -enriched BN nanoparticles grafted with poly(glycerol) exhibited efficient accumulation at the tumor sites, with a high  $^{10}\text{B}$  content of  $102.1 \mu\text{g g}^{-1}$  and a high tumor/normal tissue ratio of 7.6 at 12 h post-injection [8]. The study demonstrated the capacity to almost completely eradicate the tumors in CT26 colon carcinoma-bearing mouse models upon neutron irradiation [8].

## Cancer immunotherapy

Pathogen-associated molecular patterns (PAMPs), such as toll-like receptor (TLR) agonists, can be recognized by pattern recognition receptors (PRRs) on immune cells and activate the immune system to treat cancer [78]. For example, unmethylated cytosine-guanine dinucleotide-containing oligodeoxynucleotides (CpG-ODNs) can be recognized by TLR-9, induce Th1 cellular immune response, and have been used in many clinical trials for cancer therapy. However, the administration of free CpG-ODNs is associated with a short half-life period, easy clearance from the body, low uptake efficiency by immune cells, and limited efficacy [79]. Therefore, various particulate platforms have been developed to deliver CpG-ODNs for enhanced

immune modulation and cancer immunotherapy, such as BN nanoparticles, coordination polymers, and mesoporous silica [26, 80–82].

In 2011, Zhi and Hanagata et al. reported that BN nanospheres effectively enhanced the intracellular delivery of CpG-ODNs into 293XL-TLR9 cells and promoted the TLR9 activity, compared with free CpG-ODNs [83]. In 2012, Hanagata et al. identified a BP7 peptide with specific affinity to BN nanospheres and reported that the use of the specific BP7 peptide 5 folds increased the loading efficiency of CpG-ODNs onto BN nanospheres and significantly increased the cytokines release of tumor necrosis factor (TNF- $\alpha$ ) and interleukin-6 (IL-6) from peripheral blood mononuclear cells (PBMCs) [84]. In 2013 and 2015, Hanagata et al. reported the surface modification of BN nanospheres with chitosan and polyethyleneimine, respectively, which enhanced their loading capacity of CpG-ODNs and significantly induced the secretion of TNF- $\alpha$  and IL-6 from PBMCs [85, 86]. In 2018, Zhang et al. reported that the surface modification of BN nanospheres with amino group-grafted mesoporous silica greatly enhanced the delivery of CpG-ODNs into RAW264.7 macrophages, significantly stimulated the secretion of TNF- $\alpha$ , IL-6 and IFN- $\alpha$ , and thus inhibited the proliferation of 4T1 cancer cells using Transwell plates-based coculture system *in vitro* [26].

Moreover, inspired by the positive effects of boron supplementation on the immune system through promoting the production of cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interferon- $\gamma$  (IFN- $\gamma$ ), we developed BN nanospheres as adjuvants for cancer immunotherapy, which promoted Th1 cytokines secretion, strengthened antitumor immune response, and inhibited the distant tumor growth (unpublished data).

## Irreversible electroporation

Irreversible electroporation is a non-thermal technique for focal ablation of solid tumors by applying high-intensity electrical pulses to increase the cell transmembrane potentials, create permanent defects to disrupt the cell membranes, and induce cancer cell death.

In 2012, Raffa et al. reported that the presence of BN nanotubes locally amplified the electric field, decreased the voltage required for irreversible electroporation cancer treatment, and reduced the cell viability of cancer cells by 2.2-fold [23].

## Combination therapy

Combination cancer therapy is a promising strategy that combines different types of modalities to combat cancer and generate combined efficacy greater than that of the individual modalities. Due to their excellent biocompatibility, high loading capacity, and unique bioactivity, BN nanomaterials are an

excellent platform for integrating diverse ingredients, including chemotherapy drugs, photosensitizers, and immunopotentiators, to mediate the combination of various cancer therapeutic modalities.

In 2017, Sharker et al. reported that indocyanine green (ICG)-loaded BN particles with DOX-conjugated hyaluronic acid were developed to combine photothermal therapy and chemotherapy, generating synergistic effects to completely eradicate cancer cells *in vitro* [66]. In 2024, Li et al. reported the surface modification of BN nanoparticles with cancer cell membrane and acylated TAT peptides for the targeted code-livery of ICG and DOX to tumors to combine photothermal therapy and chemotherapy, which effectively inhibited tumor growth in mice [70].

In 2021, Li et al. reported the use of two-dimensional (2D)  $^{10}\text{B}$ -enriched BN nanosheets loaded with DOX to combine BNCT therapy with chemotherapy, generating synergistic effects to inhibit tumor growth and prolong the survival rate in triple-negative breast cancer-bearing mouse models, compared with monotherapy [67]. In 2025, Li et al. reported the assemble of  $^{10}\text{B}$ -enriched BN quantum dots with  $\text{Fe}^{3+}$  for the combination of BNCT therapy with chemodynamic therapy (CDT), generating synergistic effects to induce immunogenic cell death and suppress tumor growth in 4T1 tumor-bearing mouse models [62].

In 2023, Chen et al. reported the loading of TLR agonist R837 onto  $^{10}\text{B}$ -enriched BN nanostructures to combine BNCT therapy with cancer immunotherapy, which generated synergistic effects to destroy cancer cells, activate the antigen presenting cells, and boost antitumor immune response [68].

## Perspectives and challenges

The exploration of BN nanomaterials in cancer therapy is an emerging area with great potential and a bright future, although the research progress about this topic is still in its infancy compared to other sophisticated and clinically approved materials, such as liposomes and polymers. BN nanomaterials with high degrees of hydroxylation exhibit much higher drug loading capacity of chemotherapy drugs (such as DOX, CPT) than other nanocarrier systems, including liposomes and polymers, due to the inherent extremely light nature of BN components and the additional  $\pi$ - $\pi$  interactions between conjugated BN domains and chemotherapy drug molecules. Furthermore, BN nanomaterials have been reported to have better biocompatibility than their carbon counterparts. Most importantly, BN nanomaterials with boron components are promising for their unique bioactivities, such as the potential tumor targeting ability, intrinsic anticancer effects, and BNCT therapy. There are still many problems to be solved and much work to be done to achieve their practical application.

Despite the considerable efforts of material scientists in synthesizing BN nanomaterials over the past two decades, the challenges associated with large-scale commercialization remain significant. These challenges include the low yield, the high cost of production, and the variability of different batches. The conventional high-temperature synthesis process of BN nanomaterials is energy-intensive and not environmentally friendly. Consequently, there is a significant value in the development of novel, cost-effective, and eco-friendly synthesis processes for producing BN nanomaterials. In addition, the efficacy of BN nanomaterials in various cancer treatment modalities is closely related to their crystallinity, size, structure, and surface functional groups. The precise regulation of their physicochemical properties and the study of the relationship between their various parameters and the efficacy of different tumor treatment methods are of great significance and help to optimize material design and treatment outcomes.

So far, at least five boron-containing compounds, including Bortezomib, Tavorborole, Ixazomib, Crisaborole, and Vaborbactam, have been approved by FDA for the treatment of cancer (such as myeloma and lymphoma), infection (such as fungal and bacteria), and atopic dermatitis. Boron compounds may exhibit distinctive biological activities, including their intrinsic antitumor properties, immune system activation, promotion of osteoblast proliferation, and antibacterial and wound healing effects. BN nanomaterials possess a very high boron content, which renders them an excellent candidate for boron-based nanomedicine and cancer therapy. Although as we have summarized in this review, BN nanomaterials have effectively enhanced the efficacy of tumor treatment based on different treatment modalities in animal experiments. However, to our knowledge, no clinical trials regarding BN nanomaterials have been conducted so far. Compared with other approved nanomaterials with a history in biomedicine of more than 60 years, such as liposomes and polymers, BN nanomedicines have a much shorter research and development history of around 10 years, and only a very limited number of research groups are engaged in related research. In order to carry out relevant clinical trials, researchers still need to perform many preclinical trials, particularly comparative studies between BN system and other approved systems, to provide more evidence to prove that BN-based nanomedicines are superior to other approved delivery systems in the field of cancer treatment for certain types of cancers and treatment modalities. Based on these, researchers may convince medical regulatory agencies, clinicians, and pharmaceutical companies to conduct clinical research on BN-based nanomedicines.

The rational design and effective use of the distinct biological activity of BN nanomaterials, which differs from that of other nanomaterials, has the potential to enhance the efficacy of cancer treatment, prevent tumor recurrence, facilitate the eradication of malignant tumors, promote tissue regeneration,



and alleviate metabolic burden. We believe that conducting related fundamental research on BN in the following areas will be promising in the future. For example, the biological activities of BN nanomaterials, such as the inhibition of cancer cell proliferation, the induction of cancer cells apoptosis, and the activation of antitumor immune response, can be exploited to produce antitumor cascades of chemotherapy and immunotherapy, thereby enhancing tumor treatment effects. In addition, BN nanomaterials are expected to simultaneously achieve cancer treatment and tissue regeneration, such as bone tumors. BN nanomaterials also have the potential to be used in a combinatorial manner to treat tumors and achieve subsequent wound healing. The Lewis acidity of boron in BN nanomaterials may facilitate the formation of reversible covalent bonds with certain proteins that are over-expressed in tumors, potentially enabling targeted delivery to tumor sites. Furthermore, some BN nanomaterials possess intrinsic fluorescent imaging capacities. Consequently, BN nanomaterials hold considerable promise for utilization in integrated cancer diagnosis and treatment.

## Author contributions

XL contributed toward writing—original draft. NH and DM contributed toward supervision and writing—review & editing.

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## Data availability

Data sharing is not applicable to this review paper as no new data were created.

## Declarations

**Conflict of interest** The authors declare no conflicts of interest.

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