BIBLIOGRAPHIC INFORMATION SYSTEM

JOURNAL FULL TITLE: Journal of Biomedical Research & Environmental Sciences
ABBREVIATION (NLM): J Biomed Res Environ Sci **ISSN:** 2766-2276 **WEBSITE:** https://www.jelsciences.com

SCOPE & COVERAGE

- **Sections Covered:** 34 specialized sections spanning 143 topics across Medicine, Biology, Environmental Sciences, and General Science
- Ensures broad interdisciplinary visibility for high-impact research.

PUBLICATION FEATURES

- **Review Process:** Double-blind peer review ensuring transparency and quality
- **Time to Publication:** Rapid 21-day review-to-publication cycle
- **Frequency:** Published monthly
- **Plagiarism Screening:** All submissions checked with iThenticate

INDEXING & RECOGNITION

- **Indexed in:** Google Scholar, IndexCopernicus (**ICV 2022: 88.03**)
- **DOI:** Registered with CrossRef (**10.37871**) for long-term discoverability
- **Visibility:** Articles accessible worldwide across universities, research institutions, and libraries

OPEN ACCESS POLICY

- Fully Open Access journal under Creative Commons Attribution 4.0 License (CC BY 4.0)
- Free, unrestricted access to all articles globally

GLOBAL ENGAGEMENT

- **Research Reach:** Welcomes contributions worldwide
- **Managing Entity:** SciRes Literature LLC, USA
- **Language of Publication:** English

SUBMISSION DETAILS

- Manuscripts in Word (.doc/.docx) format accepted

SUBMISSION OPTIONS

- **Online:** https://www.jelsciences.com/submit-your-paper.php
- **Email:** support@jelsciences.com, support@jbresonline.com

HOME ABOUT ARCHIVE SUBMIT MANUSCRIPT APC

Vision: The Journal of Biomedical Research & Environmental Sciences (JBRES) is dedicated to advancing science and technology by providing a global platform for innovation, knowledge exchange, and collaboration. Our vision is to empower researchers and scientists worldwide, offering equal opportunities to share ideas, expand careers, and contribute to discoveries that shape a healthier, sustainable future for humanity.

JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
ISSN: 2766-2276
SUBJECT AREA(S): ONCOLOGY | CANCER | RADIATION THERAPY
DOI: 10.37871

REVIEW ARTICLE

Boron Neutron Capture Therapy in Cutaneous Melanoma: Novel Delivery Strategies

Mikhailova NP, Znatdinov DI* and Selyanin MA

Martinex International Research Center for Innovative Technologies, Moscow 111123, 12 bld. 32nd Vladimirskaya str, Russia

Abstract

Cutaneous Melanoma (CM), with its profound heterogeneity and capacity for therapy resistance, represents a persistent challenge in oncology. This review charts the evolution of management strategies from a refined understanding of molecular pathogenesis towards the advent of highly selective therapeutic modalities. While the foundation of modern care rests on targeting key oncogenic pathways and integrating advanced diagnostics such as PRAME and liquid biopsies, a significant development lies in the application of Boron Neutron Capture Therapy (BNCT). This binary modality achieves exceptional micro-scale selectivity through biochemical targeting, with clinical data confirming its efficacy against radioresistant disease. The forthcoming transformation in BNCT efficacy and accessibility is increasingly linked to innovations in two key areas: the transition to compact accelerator-based neutron sources and, crucially, the rational design of novel boron delivery agents. This work provides a critical analysis of the paradigm shift from low-molecular-weight compounds towards sophisticated nanoscale systems. A particular focus is placed on hyaluronic acid-based platforms engineered for active targeting via the CD44 receptor, as well as on groundbreaking approaches like elemental boron nanoparticles. The emergence of these novel constructs signals a progression towards more precise and personalized oncologic interventions. To provide a comprehensive overview, this article is structured to first examine the molecular and diagnostic landscape of cM, then detail the principles and clinical evidence for BNCT, and finally analyze the cutting-edge strategies for boron delivery, concluding with future perspectives. Thus, BNCT, augmented by these advanced delivery technologies, is positioned as a compelling and precise approach for addressing the central challenge in CM: Overcoming therapy resistance.

***Corresponding author(s)**

Znatdinov DI, Martinex International Research Center for Innovative Technologies, Moscow 111123, 12 bld. 32nd Vladimirskaya str, Russia

Email: znatdinov@martinex.ru

DOI: 10.37871/jbres2250

Submitted: 13 November 2025

Accepted: 29 December 2025

Published: 30 December 2025

Keywords

- Cutaneous melanoma
- Boron neutron capture therapy
- Targeted delivery
- Hyaluronic acid
- CD44
- Nanomedicine
- BNCT

VOLUME: 6 ISSUE: 12 - DECEMBER, 2025

Scan Me

How to cite this article: Mikhailova NP, Znatdinov DI, Selyanin MA. Boron Neutron Capture Therapy in Cutaneous Melanoma: Novel Delivery Strategies. J Biomed Res Environ Sci. 2025 Dec 30; 6(12): 2045-2067. doi: 10.37871/jbres2250, Article ID: JBRES2250, Available at: https://www.jelsciences.com/articles/jbres2250.pdf

Introduction

Within the framework of the contemporary understanding of Cutaneous Melanoma (CM) etiology and pathogenesis, a comprehensive analysis integrating risk factors with molecular-genetic mechanisms is paramount. The recent World Health Organization classification, which systematizes melanoma development pathways based on the degree of Cumulative Sun Damage (CSD), precursor lesions, and specific genetic aberrations, represents a significant advance in this field. Pathogenetically, the conversion of melanin from an antioxidant to a pro-oxidant under ultraviolet radiation initiates a cascade of oxidative stress and DNA damage. Key drivers of tumor progression include hyperactivation of the MAPK pathway-frequently driven by mutations in BRAF (~ 50%) and NRAS (15-20%) and the PI3K/PTEN/AKT pathway, alongside disruptions in cell cycle regulation (e.g., CDKN2A mutations), apoptosis, and telomere homeostasis (e.g., TERT promoter mutations). Understanding these mechanisms not only elucidates the disease's molecular basis but also underpins the development of targeted and immune-oncological therapies, which have a new treatment paradigm for advanced melanoma [1,2].

While systemic therapies have revolutionized treatment, diagnostically challenging and therapy-resistant cases persist, necessitating advanced diagnostic tools and novel therapeutic approaches [3]. In diagnostics, immunohistochemistry remains essential, particularly for dedifferentiated melanomas lacking conventional markers (S100, HMB-45, Melan-A). Here, the highly sensitive marker PRAME is invaluable, as is immunohistochemical detection of the BRAF V600E mutation, serving as a more accessible alternative to PCR. Furthermore, liquid biopsy represents a promising direction, enabling the determination of circulating microRNA profiles (e.g., miR-221, miR-146a-5p) associated with progression and therapy resistance, and the analysis of exosomes that participate in pre-metastatic niche formation. The MIA (melanoma inhibitory activity) protein is also a potential serological biomarker for monitoring. The integrated use of these multi-level biomarkers paves the way for personalized management in cM, from early diagnosis to overcoming therapy resistance[4].

Precisely for addressing the challenge of therapy resistance, Boron Neutron Capture Therapy (BNCT) emerges as a highly selective treatment modality with significant potential for localized, radioresistant skin malignancies (Figure 1) [5,6]. This method has demonstrated clinically proven high efficacy in melanoma and extramammary Paget's disease, achieving complete response rates up to 73% and long-

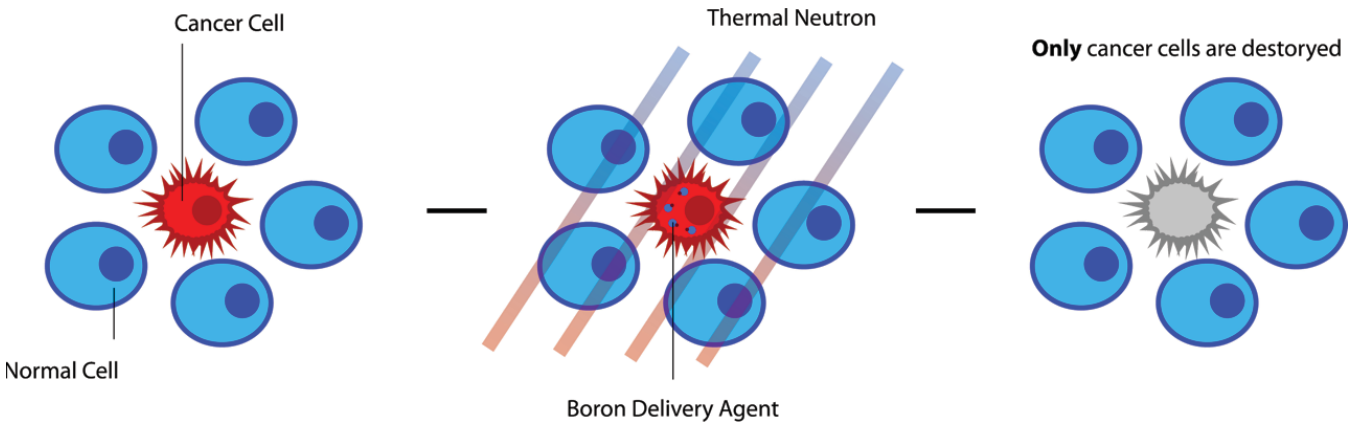

Figure 1 Schematic illustration of the Boron Neutron Capture Therapy (BNCT) mechanism.

term recurrence-free survival exceeding six years in some cases[7,8]. A key recent achievement facilitating its clinical translation is the transition from reactor-based to compact Accelerator-Based Neutron Sources (ABNS), making BNCT potentially accessible for general hospitals. The successful historical experience with BNCT in melanoma using 4-Borono-DL-Phenylalanine (BPA), corroborated by the recent successful completion of clinical trials for cutaneous angiosarcoma and melanoma, opens new avenues for treating resistant and recurrent forms of these dermato-oncological diseases [9,10].

The high therapeutic potential of BNCT for resistant and locally advanced malignancies is determined by several key features [11]: 1) its unique mechanism of action relies on biochemical, rather than purely physical, targeting, achieved through the selective accumulation of the stable boron-10 (^{10}B) isotope directly within tumor cells, often via specific transporters such as LAT1; 2) the subsequent irradiation with thermal neutrons triggers the $^{10}B(n,\alpha)^{7}Li$ nuclear reaction, which generates high Linear Energy Transfer (LET) particles, leading to the formation of complex, high-density DNA damage clusters with a low probability of repair; and 3) it enables precision treatment planning based on data from positron emission tomography with [^{18}F] FBPA, magnetic resonance imaging with boron-containing contrast agents, and secondary ion mass spectrometry for imaging and quantifying boron distribution at the subcellular level. Thus, the personalization of BNCT is achieved not only through the adaptation of radiation dose but also via the selection of an optimal boron carrier based on the molecular-genetic profile of a specific tumor, opening new perspectives for treating melanoma and other cutaneous malignancies [12,14].

The ongoing evolution of BNCT is reflected in recent patent analyses, which highlight a clear shift from low-molecular-weight compounds (e.g., boronophenylalanine, sodium borocaptate) to complex nanoscale systems with superior tumorotropism and controlled release capabilities [15,16]. This development is propelled by several key directions in current research. First is the transition from reactor-based to Accelerator-Based Neutron Sources (AB-BNCT), which mitigates the issue of radioactive waste and facilitates the installation of compact units in clinical hospitals, thereby increasing the method's accessibility. Second, novel Boron Delivery Agents (BDAs) based on nanotechnology — such as nanoparticles decorated with phenylboronic acid (NanoPBA), Boronated Porphyrin Nanocomplexes (BPN), and boron-rich polymer micelles—are being actively developed. These compounds are characterized by significantly higher tumor targeting and boron loading capacity compared to conventional BPA, and some possess the ability for intranuclear delivery, thereby maximizing the efficiency of the neutron capture reaction. Another promising innovation is the transdermal delivery of BPA using dissolving Micro Needles (PVA/BPA-F MNs), which provides a significant increase in the tumor-to-Normal Tissue (T/N) ratio and paves the way for non-invasive local therapy. Consequently, modern BNCT is evolving into a personalized, highly selective, and technically accessible form of radiation treatment [17,18]. Ultimately, the prospects for the broad clinical translation of BNCT are directly linked to the creation of next-generation agents that combine a high boron payload with a precision delivery mechanism [19].

Key strategies to enhance boron delivery involve conjugating biologically inert, boron-rich icosahedral clusters (e.g., carboranes, metallacarboranes) with targeted carrier molecules. This approach ensures a dramatic increase in boron payload while enabling precise tumor targeting. A wide range of carriers are

under active investigation, including receptor-specific peptides (e.g., targeting somatostatin receptors, integrin αvβ3, or GPCRs), proteins (e.g., albumin, leveraging the EPR effect), porphyrins (allowing for a combination with photodynamic therapy), as well as liposomal and polymeric nanoparticles. A particularly promising direction is the design of macromolecular prodrugs based on Hyaluronic Acid (HA), which facilitates receptor-dependent transport [20]. The targeting rationale for HA-based systems lies in their high-affinity interaction with the CD44 receptor, a transmembrane glycoprotein that is frequently overexpressed on cancer stem cells and contributes to therapy resistance (Figure 2) [21]. It is important to note that CD44 exists in multiple isoforms (e.g., CD44v6, CD44v8-10) which can enhance stemness and radioresistance, making it a compelling target for advanced therapeutics. A key feature of modern HA-systems is the incorporation of dual stimulus-responsive linkers, enabling controlled release of the active agent under specific tumor microenvironment conditions (e.g., pH, redox gradient) [22,23].

The promise of this approach is confirmed by experimental data, which demonstrate the low cytotoxicity of such HA-based nanogels, their efficient uptake by tumor cells *in vitro*, and significant tumor accumulation *in vivo* with a favorable distribution profile. The accumulated evidence underscores the potential of HA-based systems for BNCT [24,25]. Modern design strategies for these agents encompass three main directions: 1) systems based on native HA for physical or chemical drug conjugation; 2) modified HA derivatives with amphiphilic properties for self-assembly into micelles or polymersomes, often endowed with «smart» functions like sensitivity to the tumor microenvironment; and 3) hybrid nanocomplexes where HA serves as a biocompatible targeting ligand for other carriers (e.g., mesoporous silica, gold nanorods, chitosan), enabling synergistic combination with chemo- or photothermal therapies [26].

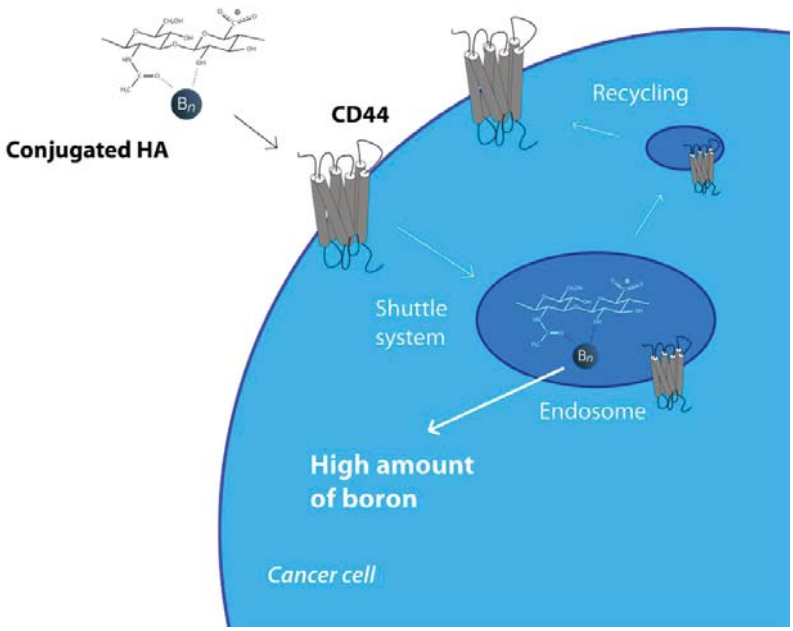

Figure 2 Receptor-mediated intracellular delivery of boron via a Hyaluronic Acid (HA)-based nanocarrier targeting CD44. The schematic shows a tumor cell within the extracellular matrix. The HA-boron conjugate specifically binds to the CD44 receptor, a glycoprotein overexpressed on many cancer cells. This interaction triggers receptor-mediated endocytosis, internalizing the boron-loaded complex into the cell within endosomal vesicles, ensuring efficient intracellular boron accumulation.

A fundamentally innovative direction in boron carrier development bypasses molecular conjugates entirely through the creation of elemental Boron Nanoparticles (eBNPs). A key innovation in their synthesis is the solid-phase stabilization of the nanoparticles with hyaluronic acid under high pressure and shear deformation, eliminating the need for additional chemical agents (Figure 3) [27,28]. The demonstrated low cytotoxicity of these eBNPs in the absence of neutron irradiation, coupled with their high radiobiological effectiveness during BNCT, positions them as a groundbreaking core component for next-generation boron capture agents.

In conclusion, BNCT emerges as a highly compelling non-invasive modality for treating early-stage cutaneous melanoma, distinguished by its exceptional efficacy and selectivity. Long-term follow-up data underscore this potential, demonstrating an excellent local control rate with complete regression of pigmented lesions following BNCT. A key and insightful observation from these clinical studies is the differential response based on pigmentation type: black macules (rich in eumelanin) often achieve complete resolution, whereas brown lesions (associated with pheomelanin) may persist. This phenomenon is likely attributable to differential boron accumulation capacities linked to distinct melanogenic pathways. The paramount advantage of BNCT lies in its micro-scale selectivity, which enables the delivery of a high, stereotactic radiation dose to the tumor (> 25 Gy-Eq) while sparing surrounding healthy tissue (skin dose ~ 18 Gy-Eq), thereby creating a wide therapeutic window. This results in a high rate of complete tumor regression without serious late complications, a critical consideration for preserving quality of life, particularly in elderly patients [29].

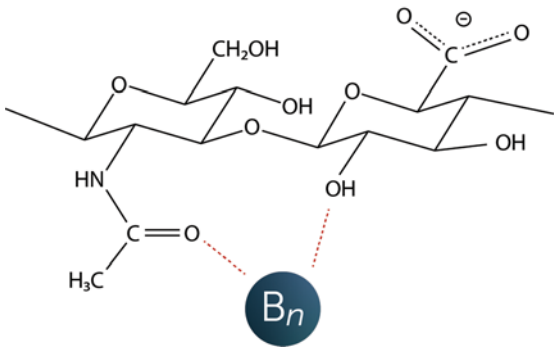

Figure 3 Schematic representation of the covalent conjugation between hyaluronic acid and a boron cluster, illustrating one strategy for developing targeted boron delivery systems. n = number of boron atoms in the particle.

BNCT constitutes a powerful and effective tool in the local management of malignant melanoma, including radioresistant forms. Its efficacy is fundamentally rooted in a unique principle of binary biological targeting, achieved through the selective intratumoral accumulation of a boron-10-containing drug and its subsequent activation with thermal neutrons. The resulting high-linear energy transfer particles induce complex, irreparable DNA damage clusters specifically within neoplastic cells. The compelling clinical outcomes, marked by high rates of local control and survival, firmly confirm BNCT's status as a promising and valuable addition to the therapeutic arsenal against melanoma [30]. Looking forward, a particularly promising direction lies in the rational design of next-generation boron carriers based on biopolymers. As previously discussed, HA serves as an ideal platform due to its inherent biocompatibility, biodegradability, and intrinsic active targeting capability via interaction with the CD44 receptor. By conjugating boron clusters to HA, it is possible to achieve significantly higher and more selective tumor accumulation compared to conventional low-molecular-weight agents like BPA. This advanced strategy promises to enhance therapeutic efficacy by increasing the boron concentration, potentially within the cell nucleus, while further minimizing off-target effects, thereby paving the way for a more precise and potent treatment for radioresistant tumors.

Despite the promising results and considerable technological advancements outlined in this review, the widespread clinical implementation of BNCT faces several significant barriers. The primary challenges include the limited availability and high cost of neutron sources, even with the transition to more compact accelerator-based systems. The development and production of novel, sophisticated boron delivery agents also contribute to the overall economic burden, necessitating future cost-effectiveness studies. Furthermore, the successful application of BNCT requires a highly specialized, multidisciplinary team encompassing radiation oncologists, medical physicists, chemists, and dermatologists, which may not be readily available in all clinical settings. Therefore, while the scientific foundation for BNCT is robust and its potential for treating resistant cutaneous melanoma is clear, overcoming these infrastructural and economic hurdles is essential for its broader translation into clinical practice. Future efforts must focus on standardizing protocols, reducing costs, and training specialized personnel to fully realize the promise of this unique binary therapy.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Strashilov S, Yordanov A. Aetiology and Pathogenesis of Cutaneous Melanoma: Current Concepts and Advances. Int J Mol Sci. 2021 Jun 15;22(12):6395. doi: 10.3390/ijms22126395. PMID: 34203771; PMCID: PMC8232613.
2. Bobos M. Histopathologic classification and prognostic factors of melanoma: a 2021 update. Ital J Dermatol Venerol. 2021 Jun;156(3):300-321. doi: 10.23736/S2784-8671.21.06958-3. Epub 2021 May 13. PMID: 33982546.
3. Bobos M. Histopathologic classification and prognostic factors of melanoma: a 2021 update. Ital J Dermatol Venerol. 2021 Jun;156(3):300-321. doi: 10.23736/S2784-8671.21.06958-3. Epub 2021 May 13. PMID: 33982546.
4. Gosman LM, Țăpoi DA, Costache M. Cutaneous Melanoma: A Review of Multifactorial Pathogenesis, Immunohistochemistry, and Emerging Biomarkers for Early Detection and Management. Int J Mol Sci. 2023 Nov 1;24(21):15881. doi: 10.3390/ijms242115881. PMID: 37958863; PMCID: PMC10650804.
5. Barth RF, Wu G, Vicente MDGH, Grecula JC, Gupta N. Boron neutron capture therapy of cancer: where do we stand now? Cancer Commun (Lond). 2024 Aug;44(8):889-892. doi: 10.1002/cac2.12581. Epub 2024 Jul 8. PMID: 38973667; PMCID: PMC11337919.
6. Cheng X, Li F, Liang L. Boron Neutron Capture Therapy: Clinical Application and Research Progress. Curr Oncol. 2022 Oct 18;29(10):7868-7886. doi: 10.3390/curroncol29100622. PMID: 36290899; PMCID: PMC9601095.
7. He H, Li J, Jiang P, Tian S, Wang H, Fan R, Liu J, Yang Y, Liu Z, Wang J. The basis and advances in clinical application of boron neutron capture therapy. Radiat Oncol. 2021 Nov 7;16(1):216. doi: 10.1186/s13014-021-01939-7. PMID: 34743756; PMCID: PMC8573925.
8. Malouff TD, Seneviratne DS, Ebner DK, Stross WC, Waddle MR, Trifiletti DM, Krishnan S. Boron Neutron Capture Therapy: A Review of Clinical Applications. Front Oncol. 2021 Feb 26;11:601820. doi: 10.3389/fonc.2021.601820. PMID: 33718149; PMCID: PMC7952987.
9. Jin WH, Seldon C, Butkus M, Sauerwein W, Giap HB. A Review of Boron Neutron Capture Therapy: Its History and Current Challenges. Int J Part Ther. 2022 Jun 9;9(1):71-82. doi: 10.14338/IJPT-22-00002.1. PMID: 35774489; PMCID: PMC9238127.
10. Kashihara T, Nakamura S, Yamazaki N, Takahashi A, Namikawa K, Ogata D, Nakano E, Okuma K, Kaneda T, Mori T, Ito K, Itami J, Shimada K, Nakagama H, Igaki H. Boron neutron capture therapy for cutaneous angiosarcoma and malignant melanoma: First in-human phase I clinical trial. Radiother Oncol. 2025 Jan;202:110607. doi: 10.1016/j.radonc.2024.110607. Epub 2024 Nov 1. PMID: 39489429.
11. Skwierawska D, López-Valverde JA, Balcerzyk M, Leal A. Clinical Viability of Boron Neutron Capture Therapy for Personalized Radiation Treatment. Cancers (Basel). 2022 Jun 10;14(12):2865. doi: 10.3390/cancers14122865. PMID: 35740531; PMCID: PMC9221296.
12. Zhou T, Igawa K, Kasai T, Sadahira T, Wang W, Watanabe

T, Bekku K, Katayama S, Iwata T, Hanafusa T, Xu A, Araki M, Michiue H, Huang P. The current status and novel advances of boron neutron capture therapy clinical trials. Am J Cancer Res. 2024 Feb 15;14(2):429-447. doi: 10.62347/HBBE6868. PMID: 38455422; PMCID: PMC10915318.

13. Bortolussi S, Liu YH, Porras I. Boron Neutron Capture Therapy: From Nuclear Physics to Biomedicine. Biology (Basel). 2021 Apr 26;10(5):370. doi: 10.3390/biology10050370. PMID: 33925863; PMCID: PMC8145707.

14. Bortolussi S, Liu YH, Porras I. Boron Neutron Capture Therapy: From Nuclear Physics to Biomedicine. Biology (Basel). 2021 Apr 26;10(5):370. doi: 10.3390/biology10050370. PMID: 33925863; PMCID: PMC8145707.

15. Zhang X, Lin Y, Hosmane NS, Zhu Y. Nanostructured boron agents for boron neutron capture therapy: a review of recent patents. Med Rev (2021). 2023 Sep 15;3(5):425-443. doi: 10.1515/mr-2023-0013. PMID: 38283251; PMCID: PMC10811353.

16. Ailuno G, Balboni A, Caviglioli G, Lai F, Barbieri F, Dellacasagrande I, Florio T, Baldassari S. Boron Vehiculating Nanosystems for Neutron Capture Therapy in Cancer Treatment. Cells. 2022 Dec 13;11(24):4029. doi: 10.3390/cells11244029. PMID: 36552793; PMCID: PMC9776957.

17. Sun Y, Wang Y, Mu S, Wu X, Yu S, Wang Z. Boron neutron capture therapy for melanoma: recent advances and future prospects. Front Oncol. 2025 Sep 1;15:1485207. doi: 10.3389/fonc.2025.1485207. PMID: 40958858; PMCID: PMC12434051.

18. Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun (Lond). 2018 Jun 19;38(1):35. doi: 10.1186/s40880-018-0299-7. PMID: 29914561; PMCID: PMC6006782.

19. Wang S, Zhang Z, Miao L, Li Y. Boron Neutron Capture Therapy: Current Status and Challenges. Front Oncol. 2022 Mar 31;12:788770. doi: 10.3389/fonc.2022.788770. PMID: 35433432; PMCID: PMC9009440.

20. Quagliariello V, Gennari A, Jain SA, Rosso F, Iaffaioli RV, Barbarisi A, Barbarisi M, Tirelli N. Double-responsive hyaluronic acid-based prodrugs for efficient tumour targeting. Mater Sci Eng C Mater Biol Appl. 2021 Dec;131:112475. doi: 10.1016/j.msec.2021.112475. Epub 2021 Oct 12. PMID: 34857264.

21. Kesharwani P, Chadar R, Sheikh A, Rizg WY, Safhi AY. CD44-Targeted Nanocarrier for Cancer Therapy. Front Pharmacol. 2022 Mar 31;12:800481. doi: 10.3389/fphar.2021.800481. PMID: 35431911; PMCID: PMC9008230.

22. Hassn Mesrati M, Syafruddin SE, Mohtar MA, Syahir A. CD44: A Multifunctional Mediator of Cancer Progression. Biomolecules. 2021 Dec 9;11(12):1850. doi: 10.3390/biom11121850. PMID: 34944493; PMCID: PMC8699317.

23. Duex J, Theodorescu D. CD44 in Bladder Cancer. Cancers (Basel). 2024 Mar 18;16(6):1195. doi: 10.3390/cancers16061195. PMID: 38539529; PMCID: PMC10969618.

24. Coninx S, Kalot G, Godard A, Bodio E, Goze C, Sancey L, Auzély-Velty R. Tailored hyaluronic acid-based nanogels as theranostic boron delivery systems for boron neutron cancer therapy. Int J Pharm X. 2022 Oct 14;4:100134. doi: 10.1016/j.ijpx.2022.100134. PMID: 36304136; PMCID: PMC9594117.

25. Krishnan V, Peng K, Sarode A, Prakash S, Zhao Z, Filippov SK, Todorova K, Sell BR, Lujano O, Bakre S, Pusuluri A, Vogus D, Tsai KY, Mandinova A, Mitragotri S. Hyaluronic acid conjugates for topical treatment of skin cancer lesions. Sci Adv. 2021 Jun 11;7(24):eabe6627. doi: 10.1126/sciadv.abe6627. PMID: 34117055; PMCID: PMC8195472.

26. Jia Y, Chen S, Wang C, Sun T, Yang L. Hyaluronic acid-based nano drug delivery systems for breast cancer treatment: Recent advances. Front Bioeng Biotechnol. 2022 Aug 24;10:990145. doi: 10.3389/fbioe.2022.990145. PMID: 36091467; PMCID: PMC9449492.

27. Selyanin MA, Khabarov VN, Boykov PY. Hyaluronic Acid: Production, properties, application in biology and medicine. UK: John Wiley & Sons; 2015. p. 215.

28. Machado V, Morais M, Medeiros R. Hyaluronic Acid-Based Nanomaterials Applied to Cancer: Where Are We Now? Pharmaceutics. 2022 Sep 30;14(10):2092. doi: 10.3390/pharmaceutics14102092. PMID: 36297526; PMCID: PMC9609123.

29. Hiratsuka J, Kamitani N, Tanaka R, Tokiya R, Yoden E, Sakurai Y, Suzuki M. Long-term outcome of cutaneous melanoma patients treated with boron neutron capture therapy (BNCT). J Radiat Res. 2020 Nov 16;61(6):945-951. doi: 10.1093/jrr/rraa068. PMID: 32990318; PMCID: PMC7674695.

30. Fukuda H. Boron Neutron Capture Therapy (BNCT) for Cutaneous Malignant Melanoma Using 10B-p-Boronophenylalanine (BPA) with Special Reference to the Radiobiological Basis and Clinical Results. Cells. 2021 Oct 26;10(11):2881. doi: 10.3390/cells10112881. PMID: 34831103; PMCID: PMC8616259.

31. Strashilov S, Yordanov A. Aetiology and Pathogenesis of Cutaneous Melanoma: Current Concepts and Advances. Int J Mol Sci. 2021 Jun 15;22(12):6395. doi: 10.3390/ijms22126395. PMID: 34203771; PMCID: PMC8232613.

32. Bobos M. Histopathologic classification and prognostic factors of melanoma: a 2021 update. Ital J Dermatol Venerol. 2021 Jun;156(3):300-321. doi: 10.23736/S2784-8671.21.06958-3. Epub 2021 May 13. PMID: 33982546.

33. Bobos M. Histopathologic classification and prognostic factors of melanoma: a 2021 update. Ital J Dermatol Venerol. 2021 Jun;156(3):300-321. doi: 10.23736/S2784-8671.21.06958-3. Epub 2021 May 13. PMID: 33982546.

34. Gosman LM, Țăpoi DA, Costache M. Cutaneous Melanoma: A Review of Multifactorial Pathogenesis, Immunohistochemistry, and Emerging Biomarkers for Early Detection and Management. Int J Mol Sci. 2023 Nov 1;24(21):15881. doi: 10.3390/ijms242115881. PMID: 37958863; PMCID: PMC10650804.

35. Barth RF, Wu G, Vicente MDGH, Grecula JC, Gupta N. Boron neutron capture therapy of cancer: where do we stand now? Cancer Commun (Lond). 2024 Aug;44(8):889-892. doi: 10.1002/cac2.12581. Epub 2024 Jul 8. PMID: 38973667; PMCID: PMC11337919.

36. Cheng X, Li F, Liang L. Boron Neutron Capture Therapy: Clinical Application and Research Progress. Curr Oncol. 2022 Oct 18;29(10):7868-7886. doi: 10.3390/curroncol29100622. PMID: 36290899; PMCID: PMC9601095.

37. He H, Li J, Jiang P, Tian S, Wang H, Fan R, Liu J, Yang Y, Liu Z, Wang J. The basis and advances in clinical application of boron neutron capture therapy. Radiat Oncol. 2021 Nov 7;16(1):216. doi: 10.1186/s13014-021-01939-7. PMID: 34743756; PMCID: PMC8573925.

38. Malouff TD, Seneviratne DS, Ebner DK, Stross WC, Waddle MR, Trifiletti DM, Krishnan S. Boron Neutron Capture Therapy: A Review of Clinical Applications. Front Oncol. 2021 Feb 26;11:601820. doi: 10.3389/fonc.2021.601820. PMID: 33718149; PMCID: PMC7952987.

39. Jin WH, Seldon C, Butkus M, Sauerwein W, Giap HB. A Review of Boron Neutron Capture Therapy: Its History and Current Challenges. Int J Part Ther. 2022 Jun 9;9(1):71-82. doi: 10.14338/IJPT-22-00002.1. PMID: 35774489; PMCID: PMC9238127.

40. Kashihara T, Nakamura S, Yamazaki N, Takahashi A, Namikawa K, Ogata D, Nakano E, Okuma K, Kaneda T, Mori T, Ito K, Itami J, Shimada K, Nakagama H, Igaki H. Boron neutron capture therapy for cutaneous angiosarcoma and malignant melanoma: First in-human phase I clinical trial. Radiother Oncol. 2025 Jan;202:110607. doi: 10.1016/j.radonc.2024.110607. Epub 2024 Nov 1. PMID: 39489429.

41. Skwierawska D, López-Valverde JA, Balcerzyk M, Leal A. Clinical Viability of Boron Neutron Capture Therapy for Personalized Radiation Treatment. Cancers (Basel). 2022 Jun 10;14(12):2865. doi: 10.3390/cancers14122865. PMID: 35740531; PMCID: PMC9221296.

42. Zhou T, Igawa K, Kasai T, Sadahira T, Wang W, Watanabe T, Bekku K, Katayama S, Iwata T, Hanafusa T, Xu A, Araki M, Michiue H, Huang P. The current status and novel advances of boron neutron capture therapy clinical trials. Am J Cancer Res. 2024 Feb 15;14(2):429-447. doi: 10.62347/HBBE6868. PMID: 38455422; PMCID: PMC10915318.

43. Bortolussi S, Liu YH, Porras I. Boron Neutron Capture Therapy: From Nuclear Physics to Biomedicine. Biology (Basel). 2021 Apr 26;10(5):370. doi: 10.3390/biology10050370. PMID: 33925863; PMCID: PMC8145707.

44. Bortolussi S, Liu YH, Porras I. Boron Neutron Capture Therapy: From Nuclear Physics to Biomedicine. Biology (Basel). 2021 Apr 26;10(5):370. doi: 10.3390/biology10050370. PMID: 33925863; PMCID: PMC8145707.

45. Zhang X, Lin Y, Hosmane NS, Zhu Y. Nanostructured boron agents for boron neutron capture therapy: a review of recent patents. Med Rev (2021). 2023 Sep 15;3(5):425-443. doi: 10.1515/mr-2023-0013. PMID: 38283251; PMCID: PMC10811353.

46. Ailuno G, Balboni A, Caviglioli G, Lai F, Barbieri F, Dellacasagrande I, Florio T, Baldassari S. Boron Vehiculating Nanosystems for Neutron Capture Therapy in Cancer Treatment. Cells. 2022 Dec 13;11(24):4029. doi: 10.3390/cells11244029. PMID: 36552793; PMCID: PMC9776957.

47. Sun Y, Wang Y, Mu S, Wu X, Yu S, Wang Z. Boron neutron capture therapy for melanoma: recent advances and future prospects. Front Oncol. 2025 Sep 1;15:1485207. doi: 10.3389/fonc.2025.1485207. PMID: 40958858; PMCID: PMC12434051.

48. Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun (Lond). 2018 Jun 19;38(1):35. doi: 10.1186/s40880-018-0299-7. PMID: 29914561; PMCID: PMC6006782.

49. Wang S, Zhang Z, Miao L, Li Y. Boron Neutron Capture Therapy: Current Status and Challenges. Front Oncol. 2022 Mar 31;12:788770. doi: 10.3389/fonc.2022.788770. PMID: 35433432; PMCID: PMC9009440.

50. Quagliariello V, Gennari A, Jain SA, Rosso F, Iaffaioli RV, Barbarisi A, Barbarisi M, Tirelli N. Double-responsive hyaluronic acid-based prodrugs for efficient tumour targeting. Mater Sci Eng C Mater Biol Appl. 2021 Dec;131:112475. doi: 10.1016/j.msec.2021.112475. Epub 2021 Oct 12. PMID: 34857264.

51. Kesharwani P, Chadar R, Sheikh A, Rizg WY, Safhi AY. CD44-Targeted Nanocarrier for Cancer Therapy. Front Pharmacol. 2022 Mar 31;12:800481. doi: 10.3389/fphar.2021.800481. PMID: 35431911; PMCID: PMC9008230.

52. Hassn Mesrati M, Syafruddin SE, Mohtar MA, Syahir A. CD44: A Multifunctional Mediator of Cancer Progression. Biomolecules. 2021 Dec 9;11(12):1850. doi: 10.3390/biom11121850. PMID: 34944493; PMCID: PMC8699317.

53. Duex J, Theodorescu D. CD44 in Bladder Cancer. Cancers (Basel). 2024 Mar 18;16(6):1195. doi: 10.3390/cancers16061195. PMID: 38539529; PMCID: PMC10969618.

54. Coninx S, Kalot G, Godard A, Bodio E, Goze C, Sancey L, Auzély-Velty R. Tailored hyaluronic acid-based nanogels as theranostic boron delivery systems for boron neutron cancer therapy. Int J Pharm X. 2022 Oct 14;4:100134. doi: 10.1016/j.ijpx.2022.100134. PMID: 36304136; PMCID: PMC9594117.

55. Krishnan V, Peng K, Sarode A, Prakash S, Zhao Z, Filippov SK, Todorova K, Sell BR, Lujano O, Bakre S, Pusuluri A, Vogus D, Tsai KY, Mandinova A, Mitragotri S. Hyaluronic acid conjugates for topical treatment of skin cancer lesions. Sci Adv. 2021 Jun 11;7(24):eabe6627. doi: 10.1126/sciadv.abe6627. PMID: 34117055; PMCID: PMC8195472.

56. Jia Y, Chen S, Wang C, Sun T, Yang L. Hyaluronic acid-based nano drug delivery systems for breast cancer treatment: Recent advances. Front Bioeng Biotechnol. 2022 Aug 24;10:990145. doi: 10.3389/fbioe.2022.990145. PMID: 36091467; PMCID: PMC9449492.

57. Selyanin MA, Khabarov VN, Boykov PY. Hyaluronic Acid: Production, properties, application in biology and medicine. UK: John Wiley & Sons; 2015. p. 215.

58. Machado V, Morais M, Medeiros R. Hyaluronic Acid-Based Nanomaterials Applied to Cancer: Where Are We Now? Pharmaceutics. 2022 Sep 30;14(10):2092. doi: 10.3390/pharmaceutics14102092. PMID: 36297526; PMCID: PMC9609123.

59. Hiratsuka J, Kamitani N, Tanaka R, Tokiya R, Yoden E, Sakurai Y, Suzuki M. Long-term outcome of cutaneous melanoma patients treated with boron neutron capture therapy (BNCT). J Radiat Res. 2020 Nov 16;61(6):945-951. doi: 10.1093/jrr/rraa068. PMID: 32990318; PMCID: PMC7674695.

60. Fukuda H. Boron Neutron Capture Therapy (BNCT) for Cutaneous Malignant Melanoma Using 10B-p-Boronophenylalanine (BPA) with Special Reference to the Radiobiological Basis and Clinical Results. Cells. 2021 Oct 26;10(11):2881. doi: 10.3390/cells10112881. PMID: 34831103; PMCID: PMC8616259.