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REVIEW ARTICLE

Advancing Medulloblastoma Treatment: Molecular Mechanisms, Drug Repurposing, and Precision Therapies

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Abstract
Medulloblastomas are the most common malignant pediatric brain tumors, representing approximately 20% of the central nervous system cancers in children. These tumors are highly heterogeneous and classified into four molecular subgroups—WNT, SHH, Group 3, and Group 4—each with distinct genetic and epigenetic profiles that influence tumor behavior, therapeutic response, and patient outcomes. Advances in molecular diagnostics have improved the subclassification of medulloblastomas, yet treatment outcomes for high-risk subtypes, particularly Group 3, remain poor, with current modalities often associated with severe long-term neurocognitive and systemic toxicities. Effective drug delivery across the blood–brain barrier remains a major hurdle, limiting the clinical efficacy of targeted therapies. Drug repurposing offers a promising strategy to accelerate treatment availability by utilizing US Food and Drug Administration-approved agents, including niclosamide, itraconazole, and arsenic trioxide, to target critical oncogenic pathways and overcome therapeutic resistance. However, challenges such as limited blood–brain barrier penetration and the lack of pediatric-specific pharmacokinetic data persist. Future research should focus on integrating comprehensive molecular profiling to guide personalized therapy selection, optimizing drug-delivery systems, and exploring rational drug combinations. Emerging technologies, including nanotechnology-based delivery systems, CRISPR-mediated gene editing, and chimeric antigen receptor-T cell therapies, hold significant potential for transforming medulloblastoma treatment paradigms but require further refinement to address toxicity, off-target effects, and biomarker development. Advancing innovative, less toxic therapeutic strategies through the integration of molecular diagnostics and precision therapies is essential to improving survival outcomes and quality of life for children with medulloblastomas.

1 Introduction

Medulloblastoma (MBs) are the most common malignant brain tumors in children, representing about 20% of pediatric central nervous system (CNS) cancers [1]. These tumors primarily affect children under 10 years of age and bring substantial challenges for treatment and long-term care. Advances in molecular profiling have led to the classification of MBs into four major subgroups—WNT, SHH, Group 3, and Group 4—each defined by specific genetic and epigenetic changes that influence tumor behavior, treatment response, and outcomes [2].

WNT-driven MBs tend to have a favorable prognosis and are associated with *CTNNB1* variants that activate the WNT/β-catenin signaling pathway. SHH-driven MBs, linked to alterations in SMO and PTCH1, have a more variable clinical course and often show resistance to targeted therapies [3]. Group 3 MBs, frequently characterized by MYC amplification and chromothripsis, are the most aggressive subtype, with high rates of metastasis and poor survival despite intensive treatment. Group 4 MBs are less aggressive but remain poorly understood because of their molecular complexity [4].

Current treatment strategies, which include surgery, radiation, and chemotherapy, have improved survival for many patients. However, these approaches are associated with serious long-term effects, including cognitive impairment, developmental delays, and an increased risk of secondary

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Key Points

Medulloblastoma is the most common malignant pediatric brain tumor, where improved molecular diagnostics have enabled precise subgroup identification, yet high-risk subtypes such as Group 3 continue to have poor outcomes with significant treatment-related toxicities.

Drug repurposing strategies, leveraging US Food and Drug Administration-approved agents to target critical oncogenic pathways identified through molecular profiling, represent a promising accelerated approach to improve therapeutic outcomes while reducing toxicity in children with medulloblastoma.

Emerging technologies, including nanotechnology-based targeted delivery systems, CRISPR-mediated gene editing, and chimeric antigen receptor-T cell therapies, integrated with molecular diagnostics and biomarker development, offer potential to transform medulloblastoma therapy toward a precision medicine approach that enhances survival and quality of life in pediatric patients.

cancers [5]. Additionally, the challenge of preventing relapse remains, particularly in high-risk subtypes such as Group 3, while the blood–brain barrier (BBB) further complicates effective drug delivery to the tumor site [6].

Developing new therapies for MB is a slow and costly process, often taking years before reaching clinical application. Against this backdrop, drug repurposing has gained attention as a practical strategy to expand treatment options for MB. By investigating US Food and Drug Administration (FDA)-approved drugs with established safety profiles, repurposing can offer a more efficient path to clinical testing and implementation [7]. Successes in other cancers, such as the use of thalidomide in multiple myeloma, illustrate the potential of this approach, while also reminding us of the importance of careful evaluation in new contexts.

In the case of MB, repurposing could help identify drugs capable of targeting key molecular pathways across different subgroups, with the potential to improve outcomes and quality of life for patients. Recent studies continue to reveal the molecular heterogeneity of MB, highlighting opportunities for tailored therapeutic strategies. Compounds such as valproic acid, metformin, and niclosamide are being explored for their potential to modulate metabolic and epigenetic pathways in MB [8]. Moving toward personalized treatments underscores the need for therapies that can overcome current limitations and address the persistent challenge of treatment resistance.

1.1 Methodology, Inclusion and Exclusion Criteria, and Risk of Bias

This narrative review examined studies published between 2008 and 2025 to explore molecular mechanisms, therapeutic strategies, and drug repurposing in MBs, with a focus on molecular targets and emerging treatments. PubMed was used to identify relevant English-language studies using keywords such as "medulloblastomas," "drug repurposing," "WNT," "SHH," "MYC amplification," "tumor microenvironment," and "blood-brain barrier."

Included studies prioritized research on key molecular pathways (WNT, SHH, MYC), conventional treatments (surgery, chemotherapy, radiation), and drug repurposing strategies involving FDA-approved agents such as niclosamide and itraconazole. Emphasis was placed on studies exploring innovative drug-delivery systems and biomarkers for personalized medicine. Excluded materials included opinion pieces and studies lacking experimental validation or clinical relevance. Preference was given to research employing robust models, including human cell lines, animal studies, and clinical data.

The methodological quality of included studies was assessed based on study design clarity, appropriate control use, and data reliability. Potential biases, including selection and reporting bias, were evaluated by examining methodological transparency, sample size justification, and the use of randomization or blinding. Variability in experimental models, patient demographics, and treatment protocols was considered in interpreting findings.

2 Molecular Pathogenesis of Medulloblastomas

Medulloblastoma development is driven by genetic alterations, dysregulated signaling pathways, epigenetic remodeling, metabolic reprogramming, and interactions with the tumor microenvironment (TME). Understanding these mechanisms is critical for identifying therapeutic targets and guiding drug repurposing strategies.

2.1 Genetic Alterations and Molecular Subgroups

Medulloblastomas are classified into four molecular subgroups—WNT, SHH, Group 3, and Group 4—each with distinct driver variants. WNT tumors frequently harbor *CTNNB1* variants and generally have a favorable prognosis, while SHH tumors involve *PTCH1* and *SUFU* variants, with *TP53* variants linked to poor outcomes. Group 3 exhibits *MYC* amplification and aggressive behavior, and Group 4 shows *MYCN* amplification and enhancer hijacking events

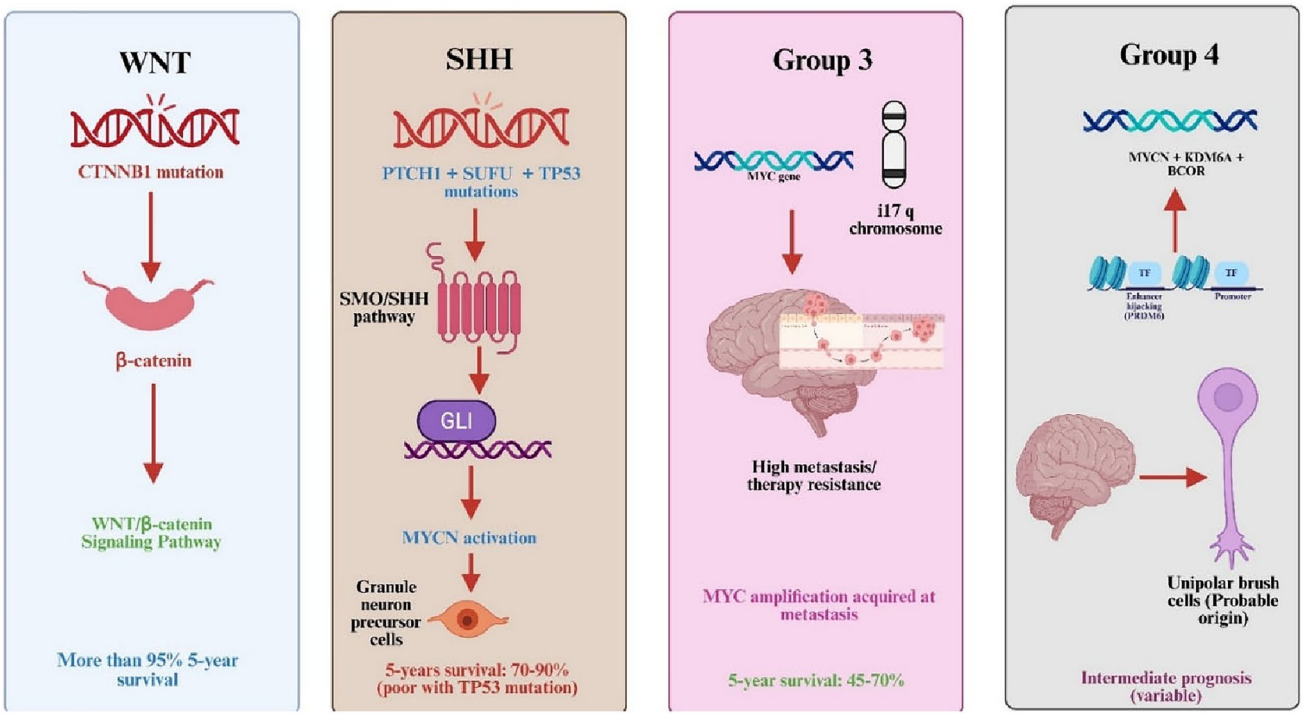

Fig. 1 Genetic alterations, signaling pathways, and prognostic implications of medulloblastoma subgroups. *BCOR* BCL6 corepressor, *CTNNB1* catenin beta 1, *i17q* isochromosome 17q, *KDM6A* lysine demethylase 6A, *MYC* myelocytomatosis, *MYCN* myelocytomatosis neuroblastoma, *PRDM6* PR/SET domain 6, *SHH* Sonic hedgehog pathway, *SMO* smoothened receptor, *TP53* tumor protein 53, *WNT* wingless/integrated pathway

promoting tumor progression. These subgroup-specific alterations inform precision therapeutic approaches and drug repurposing opportunities (Fig. 1) [9–11].

2.2 Oncogenic Signaling Pathways

Key dysregulated signaling pathways, including SHH, PI3K/AKT/mTOR, and MYC-driven transcriptional programs, drive tumor growth and therapy resistance. Activation of PI3K/AKT/mTOR promotes proliferation and mediates resistance to standard therapy, making it a target for repurposed inhibitors. MYC and *NMYC* amplify metabolic and stemness pathways that can be leveraged for targeted therapy (Fig. 2) [12, 13].

2.3 Epigenetic and RNA-Level Regulation

Epigenetic remodeling and RNA-based regulation maintain oncogenic signaling and stemness. DNA methylation and histone modifications suppress tumor suppressors, while non-coding RNAs sustain survival signaling and therapy resistance. Epigenetic regulators and RNA-modifying enzymes represent emerging pharmacological targets [16, 17].

2.4 Tumor Microenvironment and Therapy Resistance

The TME contributes to immune evasion, therapeutic resistance, and metastasis. SHH-driven tumors feature microglia-mediated immune suppression, Group 3 tumors are immunologically "cold," and WNT tumors exhibit partial immune activation. Exosomes and cytokine-mediated communication further support tumor survival and spread. Targeting these interactions, including angiogenesis and immune checkpoints, is a promising strategy for repurposed drugs (Fig. 3) [18, 19].

2.5 Metabolic Reprogramming

Metabolic adaptations, including aerobic glycolysis, glutamine dependency, and lipid metabolism, support tumor growth and therapy resistance. MYC-driven metabolic pathways in aggressive subgroups create vulnerabilities exploitable by metabolic inhibitors or repurposed drugs [20].

2.6 Cancer Stem Cells and Adaptive Resistance

Cancer stem cells contribute to recurrence and chemoresistance through self-renewal and survival within protective

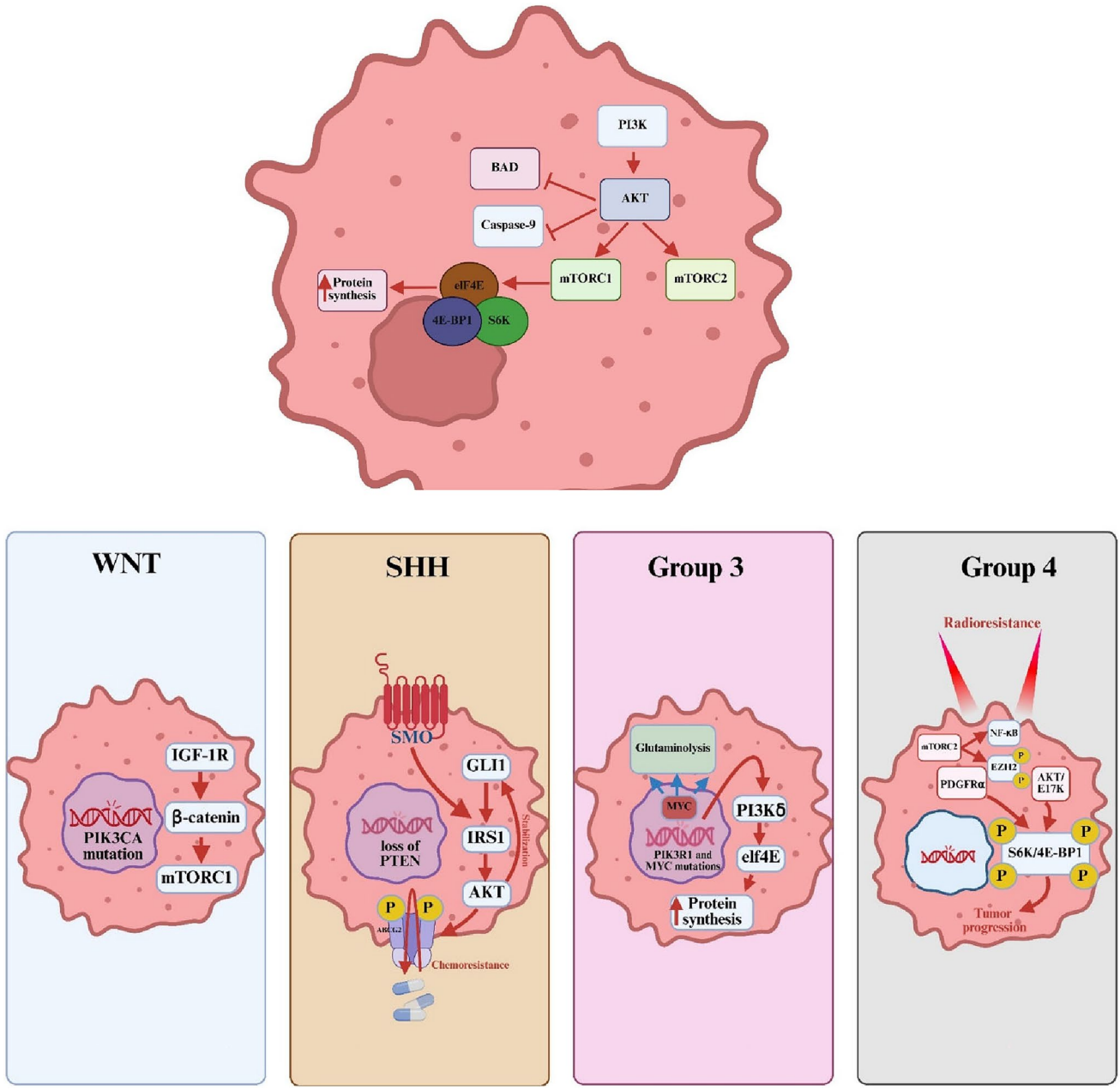

Fig. 2 Phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) signaling pathway in medulloblastoma subgroups. *4EBP1* eukaryotic translation initiation factor 4E-binding protein 1, *ABCG2* ATP-binding cassette subfamily G member 2, *BAD* Bcl-2 associated death promoter, *eIF4E* eukaryotic translation initiation factor 4E, *EZH2* enhancer of Zeste homolog 2, *GLI1* GLI Family Zinc Finger 1 Transcription Factor, *IGF-1R* insulin-like growth factor 1 receptor, *IRS1* insulin receptor substrate 1, *MYC* myelocytomatosis oncogene, *MYCN* myelocytomatosis neuroblastoma oncogene, *NF-κB* nuclear factor kappa B, *PDGFRα* platelet-derived growth factor receptor alpha, *PIK3CA* phosphoinositide 3-kinase catalytic subunit alpha, *PIK3R1* phosphoinositide 3-kinase regulatory subunit 1, *PTEN* phosphatase and tensin homolog, *S6K* ribosomal protein S6 kinase, *SHH* Sonic Hedgehog, *SMO* Smoothened Receptor, *WNT* Wingless-Integrated

niches. SHH, Group 3, and Group 4 tumors harbor distinct stem cell populations that rely on epigenetic and metabolic adaptations. Targeting stemness-associated pathways can enhance therapeutic durability and is relevant for drug repurposing strategies [21].

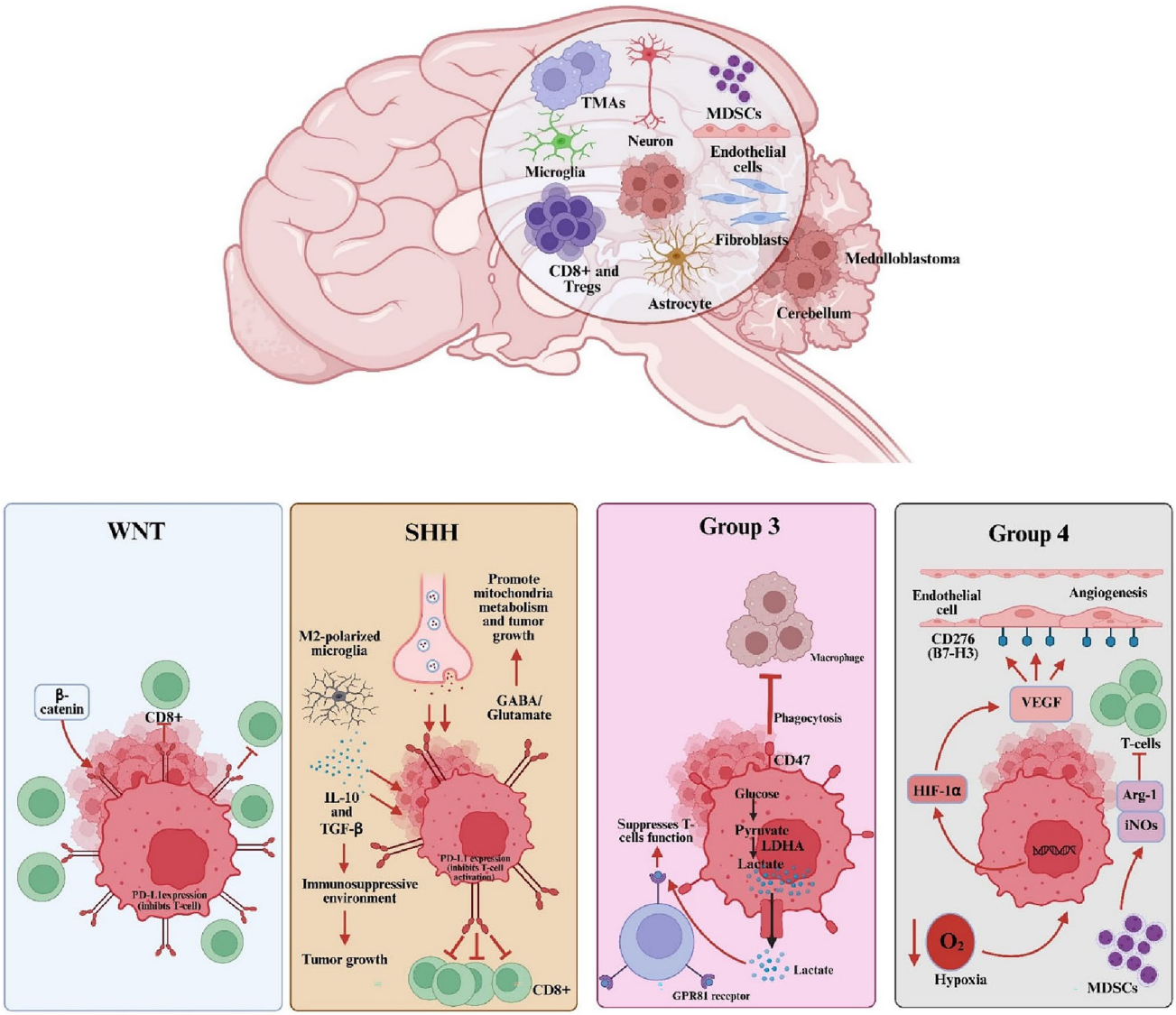

Fig. 3 Tumor microenvironment and immune evasion mechanisms across medulloblastoma subgroups. *Arg-1* arginase 1, GABA gamma-aminobutyric acid, GPR81 G-protein-coupled receptor 81, *HIF-1α* hypoxia-inducible factor 1 alpha, *IL-10* interleukin-10, *iNOS* inducible nitric oxide synthase, *LDHA* lactate dehydrogenase A, *MDSC* myeloid-derived suppressor cell, *PD-L1* programmed death ligand 1, *SHH* Sonic Hedgehog, *TGF-β* transforming growth factor beta, *VEGF* vascular endothelial growth factor, *WNT* Wingless/Integrated

3 Current Therapies for Medulloblastomas

3.1 Risk Stratification and Current Standard Therapy

Risk stratification plays a critical role in MB management, guiding therapy for both average- and high-risk patients [22]. Average-risk patients (non-metastatic, gross-total resection with ≤ 1.5 cm^2 residual tumor) typically receive maximal safe resection followed by 23.4 Gy of craniospinal irradiation (CSI) with a 54-Gy tumor bed boost. Proton therapy is preferred to limit late neurocognitive effects [23]. Concurrent vincristine is administered during radiation, followed by adjuvant multi-agent chemotherapy, as established in the COG ACNS0331 trial [24].

High-risk patients (metastatic disease or a > 1.5-cm^2 residual tumor) receive higher CSI doses (36–39.6 Gy) combined with chemotherapy. In the COG ACNS0332 trial, the addition of carboplatin during CSI improved survival outcomes specifically in patients with metastatic Group 3 MB, while the addition of isotretinoin during maintenance showed no survival benefit. The St. Jude risk-adapted approach uses higher CSI doses and dose-intensified chemotherapy (cisplatin, cyclophosphamide, vincristine) with stem-cell support, achieving good survival but with significant late toxicities [24].

The primary contributor to long-term morbidity is CSI and whole-brain radiation exposure, which drive neurocognitive decline, endocrine dysfunction, and cerebrovascular complications. Ongoing efforts aim to de-escalate the CSI dose and boost volume and to incorporate biologically targeted therapies to maintain survival while minimizing treatment-related toxicity.

3.2 Subgroup-Specific Targeted Therapies

To address the limitations of conventional treatments, subgroup-specific targeted therapies are being developed to exploit the unique molecular characteristics of each MB subgroup. In SHH-driven MBs, SMO inhibitors such as vismodegib and glasdegib have shown a 50% response rate in cases harboring *PTCH1* variants, though resistance often arises due to *TP53* or *SUFU* variants [25]. Agents targeting *GLI1/2*, such as arsenic trioxide and GANT-61, show promise in phase I trials but are limited by toxicity concerns [26].

For Group 3 tumors, *MYC* amplification is a critical therapeutic target, with preclinical studies of *MYC* inhibitors such as MYCi975 demonstrating potential, though challenges with BBB penetration persist [27]. CDK4/6 inhibitors such as ribociclib, in combination with gemcitabine, are under investigation in phase I trials, but hematologic toxicity remains a concern [28].

In Group 4, EZH2 inhibitors such as tazemetostat have shown promise, particularly in tumors harboring *KDM6A* variants [29]. Targeting *PRDM6* and *OTX2* is also under investigation, with CDK9 inhibitors and *OTX2*-small interfering RNA nanoparticles demonstrating preclinical potential, although delivery and off-target effects currently limit their application [30].

WNT-driven MBs, characterized by low recurrence rates, have been explored using therapies that target β-catenin/TCF signaling, such as the PORCN inhibitor LGK974 in phase I trials, although efficacy has been limited [31]. Anti-*DKK1* monoclonal antibodies, such as DKN-01, remain in preclinical stages and will likely require combination strategies for effectiveness [32]. Additional approaches, including targeting the PI3K/mTOR pathway with sonolisib and using SMO inhibitors, are being evaluated, though issues such as hyperglycemia present limitations [33].

These targeted therapies aim to improve outcomes while reducing treatment-related toxicities (Table 1). However, challenges including drug resistance, limited BBB penetration, and treatment-related adverse effects continue to hinder widespread clinical implementation, motivating exploration of complementary immunotherapy and advanced delivery strategies.

3.3 Emerging Immunotherapies

Building upon targeted approaches, emerging immunotherapies offer potential to enhance specificity while reducing systemic toxicity in MB treatment. Checkpoint inhibitors such as pembrolizumab have shown limited efficacy in early trials; however, combination strategies with nivolumab and ipilimumab alongside radiation are under investigation to improve immune activation [34, 35]. Chimeric antigen receptor-T cell (CAR-T) therapies, including GD2-CAR-T and B7-H3-CAR-T, are in phase I trials for recurrent MB, with the latter engineered to improve CNS penetration [36].

Oncolytic viruses such as DNX-2401 are being evaluated in phase I trials for recurrent tumors, showing potential for tumor-selective targeting [7]. Advanced checkpoint strategies, including TIM-3 inhibition with MBG453 and LAG-3 blockade with relatlimab, are planned for pediatric trials to address T-cell exhaustion, particularly in Group 3 MBs [37]. To overcome BBB limitations, localized delivery of PD-L1 nanobodies via intrathecal administration is being tested [38].

CAR-T platforms are evolving with dual-targeting bispecific CARs (e.g., B7-H3 + GD2) to prevent antigen escape and armored CAR-T that secrete interleukin-15/interleukin-21 to enhance persistence in immunosuppressive tumor environments [39]. Central nervous system-optimized CAR-T designs, such as *CXCR4*-overexpressing CAR-T, demonstrate improved migration to leptomeningeal metastases in preclinical studies [14, 15].

Oncolytic virus innovations, including tumor-selective viruses such as Delta-24-RGD and HSV-1 G207, have been engineered to enhance immune responses against CNS tumors, while microRNA-controlled viruses offer CNS-specific replication to spare peripheral tissues [40]. Bispecific antibodies, including B7-H3 x CD3 T-cell engagers, are demonstrating early promise for cerebrospinal fluid (CSF) clearance in phase I studies [41], while dual checkpoint inhibition with PD-1/TIGIT bispecific antibodies has shown superior activity in preclinical models [42].

Vaccine strategies targeting neoantigens such as *EGFRvIII* and dendritic cell vaccines leveraging CMV antigen mimicry are under early investigation and show immune activation potential [43]. Additionally, myeloid-targeting approaches, including *CSF1R* inhibition and *CD47* blockade, aim to reprogram TAMs to support anti-tumor immunity [34]. These immunotherapies represent a rapidly evolving area of MB treatment (Table 1), aiming to complement targeted therapies while addressing resistance and recurrence challenges.

Table 1 Current standard-of-care targeted immunotherapy, and novel delivery strategies for medulloblastoma, organized by treatment category

Category	Therapy	Phase of clinical trials
Standard-of-care by risk stratification	Maximal safe resection with less than 1.5 cm^2 of residual tumor	Standard of care
	Craniospinal irradiation (23.4 Gy) + tumor bed boost (54 Gy)	
	Proton therapy for reducing neurocognitive side effects	
	Chemotherapy with cisplatin, lomustine, vincristine, and cyclophosphamide	
High-risk patients	CSI doses from 36-39.6 Gy	
	High-dose chemotherapy (carboplatin, thiotepa) with autologous stem cell rescue	
	Methotrexate (controversial because of leukoencephalopathy risk)	
	SMO inhibitors (vismodegib, glasdegib) for SHH-driven tumors	Phase I trials
Subgroup-specific targeted therapies	Arsenic trioxide for GLI1/2 targeting	Phase I trials
	GANT-61 for GLI1/2 targeting	Phase I trials
	MYC inhibitors (MYCi975)	Preclinical studies
	CDK4/6 inhibitors (ribociclib) combined with gemcitabine	Phase I trials
	EZH2 inhibitors (tazemetostat)	Preclinical studies
	Targeting PRDM6 and OTX2 in Group 4	Phase I trials
	β-catenin/TCF signaling inhibition with LGK974	Phase I trials
	Anti-DKK1 monoclonal antibodies (DKN-01)	Preclinical studies
Emerging immunotherapies	PI3K/mTOR inhibitors (sonolisib) for WNT-driven tumors	Phase I trials
	SMO inhibitors for WNT-driven tumors	Phase I trials
	Checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab)	Phase I trials
	CAR-T therapies (GD2-CAR-T, B7-H3-CAR-T)	Phase I trials
	Oncolytic viruses (DNX-2401)	Phase I trials
	TIM-3 inhibitors (MBG453)	Phase I trials
	LAG-3 inhibitors (relatlimab)	Phase I trials
	PD-L1 nanobodies for CNS delivery	Phase I trials
	Dual-targeting bispecific CAR-T (B7-H3 + GD2)	Phase I trials
	Armored CAR-T (IL-15/IL-21)	Phase I trials
	CXCR4-overexpressing CAR-T for leptomeningeal metastases	Preclinical studies
	Oncolytic viruses (delta-24-RGD, HSV-1 G207)	Preclinical studies
	MicroRNA-controlled oncolytic viruses	Phase I trials
	T-cell engagers (B7-H3 × CD3)	Phase I trials
Novel drug-delivery strategies	Dual checkpoint inhibition with PD-1/TIGIT bispecific antibodies	Phase I trials
	Neoantigen vaccines targeting EGFRvIII+ MB	Preclinical studies
	Dendritic cell vaccines exploiting CMV antigen mimicry	Phase I trials
	CSF1R inhibitors	Preclinical studies
	CD47 blockade for macrophage reprogramming	Preclinical studies
	Receptor-mediated transcytosis (paclitaxel coated with Angiopep-2)	Preclinical studies
	Trojan horse approach with neutrophil carriers	Phase I trials
	Focused ultrasound with carboplatin	Phase I trials
	Convection-enhanced delivery	Phase I trials
	Intrathecal nanogels for sustained release	Preclinical studies
	Gliadel implantable wafers	Preclinical studies
	Gold nanoparticles for radiation sensitization	Preclinical studies
	Extracellular vesicles for siRNA delivery	Preclinical studies
	Dendrimers for methotrexate delivery	Phase I trials
	pH-sensitive liposomes for drug delivery	Preclinical studies and Phase I trails
	MMP-activated nanoparticles	Preclinical studies and Phase I trails
	Redox-responsive paclitaxel delivery	Preclinical studies
	Neural stem cells for tumor-homing delivery	Preclinical studies
	Macrophage carriers for adenovirus delivery	Preclinical studies

BBB blood–brain barrier, *CAR-T* chimeric antigen receptor T-cell, *CSF1R* colony-stimulating factor 1 receptor, *EGFRvIII* epidermal growth factor receptor variant III, *CSI* craniospinal irradiation, *GLI* glioma-associated oncogene, *MB* medulloblastoma, *MMP* matrix metalloproteinase, *PD-L1* programmed death-ligand 1, *siRNA* small interfering RNA, *SMO* Smoothened, *TIGIT* T-cell immunoglobulin and ITIM domain

3.4 Novel Drug-Delivery Strategies

While emerging therapies expand treatment possibilities, effective delivery across the BBB remains a critical challenge in MB management. Novel drug-delivery strategies aim to improve drug accessibility to the CNS while minimizing systemic toxicity.

Receptor-mediated transcytosis strategies, such as paclitaxel conjugated with Angiopep-2 targeting *LRP1*, have been explored in phase II trials, although some candidates such as GRN1005 were discontinued because of limited efficacy [44]. The Trojan horse approach using leukocyte carriers, such as neutrophils to deliver doxorubicin, remains in preclinical development [45].

Focused ultrasound, which transiently disrupts the BBB using microbubbles, has been evaluated in phase I trials in combination with carboplatin for recurrent tumors [4, 5]. Convection-enhanced delivery bypasses the BBB via direct catheter infusion, with drugs such as topotecan and *IL-13-PE38QQR* tested in phase I trials [7]. Intrathecal nanogels for sustained drug release into the CSF remain in preclinical stages [46], while implantable wafers, such as Gliadel®, are used off-label for localized treatment in recurrent MB [47].

Advanced nanoparticle platforms offer precise targeted delivery. Gold nanoparticles have been explored for radiation sensitization and drug delivery in preclinical models [48], while extracellular vesicles and dendrimers enable small interfering RNA and methotrexate delivery, respectively, demonstrating BBB penetration and controlled release. Stimuli-responsive delivery systems, including pH-sensitive liposomes and *MMP*-activated nanoparticles, enable tumor-selective drug release in acidic or enzyme-rich microenvironments. Redox-responsive nanoparticles triggered by glutathione within tumor cells are being explored for paclitaxel delivery [49].

Cellular delivery vehicles, including neural stem cells with tumor-homing capabilities and macrophage carriers, are being investigated for delivering oncolytic adenoviruses and histone deacetylase inhibitors in preclinical studies [32, 50]. These advanced delivery strategies (Table 1) are integral to translating novel targeted and immunotherapeutic agents into effective treatments by enhancing CNS penetration, precision, and safety profiles in MB therapy.

4 Emerging Technologies in Medulloblastoma Management

Recent advances in emerging technologies are reshaping the landscape of MB management, spanning diagnostics, monitoring, treatment development, and surgical intervention to improve patient outcomes.

4.1 Liquid Biopsy and Molecular Monitoring

Liquid biopsy technologies are becoming valuable tools for minimally invasive molecular monitoring in MB, facilitating disease status assessment, minimal residual disease detection, and personalized therapy guidance [51]. Cerebrospinal fluid-based circulating tumor DNA profiling enables early relapse detection and minimal residual disease surveillance with high sensitivity, particularly for alterations such as *MYC* amplifications [52]. Exosomal RNA analysis supports real-time evaluation of therapy response and aids molecular subgroup classification, including identifying *GLI1* splice variants in SHH-driven tumors [53]. Additionally, epigenetic fingerprinting of CSF-derived nucleic acids provides insights into subgroup-specific variants, such as *KDM6A* alterations in Group 4, using minimal sample volumes [54]. Together, these advancements highlight the potential of a liquid biopsy to enhance precision diagnostics and enable dynamic disease monitoring during treatment.

4.2 Artificial Intelligence Solutions

Building upon molecular monitoring advances, artificial intelligence (AI) technologies are transforming MB care by enabling more accurate and efficient diagnostics and treatment planning [55]. Radiomics-based AI platforms utilize magnetic resonance imaging data to classify molecular subgroups with high accuracy, potentially reducing the need for invasive biopsies [56]. Drug synergy algorithms analyze large datasets to identify effective therapeutic combinations, improving responses in patient-derived xenograft models and supporting the design of targeted treatment regimens [57]. In pathology, AI-driven tools standardize immunohistochemical scoring, such as for *TP53*, enhancing the reliability of risk stratification, particularly in SHH subgroups [58]. These AI-driven solutions contribute to precise, data-informed clinical decision making and demonstrate potential for routine clinical integration in MB management [59].

4.3 Gene Editing and Epigenetic Tools

To complement diagnostic and planning advancements, gene editing and epigenetic modulation strategies are expanding therapeutic possibilities in MB research [60]. CRISPR-Cas9 delivered via lipid nanoparticles has achieved approximately 80% editing efficiency for *MYC* knockout in Group 3 tumors in preclinical studies using intravenous delivery. Base editing approaches with AAV9 vectors have shown proof-of-concept in vitro for correcting *TP53* R175H variants in SHH-driven MBs [61]. Additionally, *DNMT3A*-targeted PROTACs, which degrade DNA methyltransferases using small molecules recruiting cereblon, are advancing through lead optimization [62]. These gene editing and epigenetic

technologies hold potential to directly modify genetic drivers and epigenetic regulators of MBs, paving the way for targeted and precise therapeutic interventions.

4.4 Organoid Models

Organoids derived from patient tumors, xenografts, or induced pluripotent stem cells have emerged as powerful models for pediatric brain tumors, offering a level of biological fidelity that surpasses conventional two-dimensional cultures. Patient- and xenograft-derived organoids retain the genetic alterations, histopathology, and molecular signatures of their parental tumors, including hallmark drivers such as SHH mutations and MYC amplification. This makes them especially valuable for investigating tumor initiation, progression, and therapy responses in MB [63]. Importantly, while patient-derived organoids allow for direct study of patient-specific mutations and drug sensitivities, xenograft-derived organoids add the capacity to model tumor growth and host–tumor interactions within an in vivo context [63].

Beyond faithfully recapitulating tumor biology, these models expand experimental possibilities. Organoids provide platforms for testing both conventional chemotherapies and novel targeted therapies directed against pathways such as SHH, PI3K/AKT, and MAPK, while also enabling the identification of resistance mechanisms [64]. Their use in lineage tracing has deepened insights into the behavior of cancer stem cells, which are critical mediators of relapse and treatment resistance [65]. Co-culture approaches further enrich these models by incorporating stromal, immune, and endothelial components, thereby allowing the study of tumor–microenvironment interactions that influence drug responses and immune evasion. Similarly, implantation of organoids into immunocompromised mice supports in vivo assays that reveal tumor growth dynamics and therapy outcomes in a physiologically relevant system [66].

Recent innovations highlight the translational potential of these approaches. For example, co-culturing SHH MB cells with cerebellar organoids has demonstrated reciprocal activation of the SHH pathway, driving malignant traits such as invasiveness and therapy resistance [67]. Likewise, human induced pluripotent stem cell-derived tumor organoids enable the modeling of recurrence and the evaluation of new therapeutic strategies, such as the OLIG2 inhibitor CT-179, which shows promise in suppressing tumor relapse [68]. Taken together, these models represent a critical step toward precision medicine in MB. However, challenges remain, including variability in organoid generation protocols, limited scalability for high-throughput drug screening, and incomplete recapitulation of systemic immune interactions. Addressing these limitations will be essential to fully translate the promise of organoid systems into clinically actionable insights.

4.5 Imaging and Surgical Innovations

Alongside molecular and therapeutic advances, imaging and surgical innovations are enhancing tumor detection and surgical precision in MB management. Intraoperative use of 5-ALA fluorescence improves visualization of tumor margins, increasing gross-total resection rates, with phase III trials in progress [69]. Raman spectroscopy, currently in prototype testing, enables real-time subgroup identification during surgery in under 5 minutes, potentially facilitating intraoperative decision making [70]. Hyperpolarized magnetic resonance imaging, under phase I investigation, offers metabolic imaging of lactate and pyruvate levels for early treatment response assessment [71]. These innovations collectively improve surgical accuracy and provide real-time insights into tumor biology, supporting better outcomes for patients.

4.6 Clinical Trial Paradigms

Innovations in clinical trial paradigms are further accelerating drug testing and treatment personalization in MB. Central nervous system drug accelerator programs prioritize CNS-active drug leads using BBB penetration scoring, as demonstrated by the Pediatric Preclinical Testing Consortium [72]. The use of three-dimensional bioprinted models to create patient-specific TMEs enables rapid screening of over 20 drug combinations within 2 weeks, potentially replacing traditional patient-derived xenograft models [73]. Additionally, digital twin trials leveraging AI to simulate treatment outcomes are underway, offering predictions for optimized therapies such as individualized CSI dosing, with pilot phases in progress at St. Jude [74]. These novel paradigms aim to accelerate the development of effective personalized treatments, enhancing the translational pathway for MB therapies.

5 The Potential of Drug Repurposing in Medulloblastoma Therapy

Drug repurposing offers considerable promise for MB treatment by leveraging existing safety data to enable faster clinical translation at lower costs — typically 60–80% less than developing new therapeutics. Many repurposed drugs already approved for CNS use can penetrate the BBB, making them suitable candidates for brain tumors such as MB. Nonetheless, challenges including limited pharmacokinetic data for pediatric dosing and patent-related barriers can hinder broad clinical adoption. Despite these

limitations, drug repurposing remains a valuable strategy to accelerate effective treatment development for MB.

5.1 Promising Repurposed Drugs for Medulloblastoma by Subgroup

5.1.1 WNT Subgroup

For the WNT subgroup, repurposed agents such as niclosamide, digoxin, and pyrvinium are under investigation for their potential to target critical pathways in tumorigenesis. Niclosamide, initially an anti-helminthic, inhibits WNT/β-catenin signaling, blocks STAT3, and induces mitochondrial stress, demonstrating promise in phase I trials for reducing metastatic spread and enhancing radiosensitivity [75]. Digoxin, a cardiac glycoside, destabilizes MYC messenger RNA and inhibits Na^+/K^+-ATPase, thereby reducing oxidative phosphorylation, with preclinical data supporting its use against residual tumor cells post-resection [76]. Pyrvinium, an anti-parasitic agent, activates CK1α to degrade β-catenin and disrupt WNT transcriptional complexes, showing potential synergy with niclosamide, though it remains in preclinical stages [31]. These agents present opportunities for adjuvant treatment within the WNT-activated subgroup, aiming to improve outcomes despite its generally favorable prognosis (Table 2).

5.1.2 SHH Subgroup

In the SHH-activated subgroup, resistance to SMO inhibitors remains a significant therapeutic challenge. Several repurposed drugs are being evaluated to target tumor progression mechanisms and overcome resistance. Itraconazole, an antifungal agent, inhibits non-canonical SMO signaling, promotes *GLI1* degradation, and blocks vascular endothelial growth factor-mediated angiogenesis, with phase I trials exploring its role as salvage therapy for vismodegib-resistant tumors [77]. Arsenic trioxide, used in acute myeloid leukemia, induces *GLI1/2* ubiquitination, generates reactive oxygen species, and promotes apoptosis via promyelocytic leukemia protein (PML) degradation, with phase II data supporting its efficacy in combination with SMO inhibitors for *TP53*-wild-type tumors [78]. Tamoxifen, a selective estrogen receptor modulator, inhibits PKCδ, blocks non-canonical SHH activation, and modulates estrogen receptors, showing preclinical potential for tumors with *SUFU* variants [79]. Fluoxetine, a selective serotonin reuptake inhibitor, destabilizes *MYC* via HDAC6 inhibition, enhances autophagy, and reduces cancer stem cell viability, with synergy noted alongside BET inhibitors in preclinical models [80]. Collectively, these agents offer strategies to improve treatment outcomes within the SHH subgroup (Table 2).

5.1.3 Group 3 Subgroup

Group 3 MBs, characterized by MYC amplification, present an urgent need for effective therapies. Repurposed agents under exploration include doxycycline, chloroquine, propranolol, and auranofin. Doxycycline, an antibiotic, inhibits mitochondrial translation and suppresses MYC expression, with a clinical trial scheduled for 2024 [81]. Chloroquine, an antimalarial agent, disrupts autophagy and lysosomal function, sensitizing tumors to radiotherapy, and is under phase I evaluation [82]. Propranolol, a beta-blocker, suppresses vascular endothelial growth factor and hypoxia-inducible factor-1 alpha, providing anti-metastatic effects supported by retrospective analyses [83]. Auranofin, used for rheumatoid arthritis, induces ferroptosis by inhibiting thioredoxin reductase and demonstrates immunomodulatory properties in phase I studies [84]. Additionally, combining doxycycline with BET inhibitors has shown synergistic MYC suppression in preclinical models, highlighting potential therapeutic avenues for this high-risk subgroup (Table 2).

5.1.4 Group 4 Subgroup

In Group 4 MBs, drug repurposing is focused on targeting epigenetic and metabolic dysregulation. Valproic acid, an antiepileptic agent, inhibits HDACs, promotes radiosensitization and cellular differentiation, and has shown improved event-free survival when combined with chemotherapy in phase II studies [85]. Metformin, widely used in diabetes mellitus management, targets mitochondrial complex I, induces energy stress, and activates AMPK, with preclinical evidence supporting its role in addressing *KDM6A*-linked metabolic abnormalities [86]. Hydralazine, an antihypertensive agent, induces DNA demethylation, reactivates *PRDM6*, and reduces chemotherapy resistance in preclinical studies [87] . These agents align with the mechanistic vulnerabilities of Group 4 MBs, with combinations such as valproic acid and radiotherapy demonstrating potential for enhanced treatment efficacy (Table 2).

5.1.5 Pan-Subgroup Agents

Several repurposed agents with multi-target activity across MB subgroups are under investigation. Losartan, an antihypertensive agent, inhibits transforming growth factor-β, reduces fibrosis, and normalizes tumor vasculature, improving drug delivery in preclinical models [88]. Atorvastatin, used for hyperlipidemia, blocks RAS/RAF signaling via HMG-CoA inhibition, demonstrating anti-angiogenic effects that may reduce leptomeningeal dissemination [89]. Disulfiram, an alcohol dependence treatment, generates reactive oxygen species through ALDH inhibition and induces copper-dependent apoptosis, with potential for targeting

Table 2 Repurposed drugs for medulloblastoma treatment by subgroup

Subgroup	Repurposed drug	Mechanism of action	Therapeutic potential	Phase
WNT subgroup	Niclosamide	Inhibits WNT/β-catenin signaling, blocks STAT3, induces mitochondrial stress	Prevents metastatic spread, enhances radiation sensitivity	Phase I trials
	Digoxin	Destabilizes MYC mRNA, inhibits Na^+/K^+-ATPase, reduces oxidative phosphorylation	Targets residual tumor cells post-resection	Preclinical data
	Pyrvinium	Activates CK1α to degrade β-catenin, disrupts WNT transcriptional complexes	Synergistic potential when combined with niclosamide	Preclinical stages
SHH subgroup	Itraconazole	Inhibits non-canonical SMO signaling, promotes GLI1 degradation, blocks angiogenesis via VEGF	Salvage therapy for vismodegib-resistant tumors	Phase I trials
	Arsenic trioxide	Induces GLI1/2 ubiquitination, generates ROS, triggers apoptosis through PML degradation	Effective in TP53-wildtype tumors, especially when combined with SMOi	Phase II evidence
	Tamoxifen	Inhibits PKCδ, blocks non-canonical SHH activation, modulates estrogen receptors	Preclinical potential for tumors with SUFU mutations	Preclinical studies
	Fluoxetine	Destabilizes MYC via HDAC6 inhibition, enhances autophagy, reduces cancer stem cell survival	Synergy with BET inhibitors	Preclinical studies
Group 3 (MYC driven)	Doxycycline	Inhibits mitochondrial translation, suppresses MYC, reduces oxidative phosphorylation	Targets MYC-driven tumors, reducing oxidative stress, pre-trial planned for 2024	Planned clinical trial
	Chloroquine	Blocks autophagy and lysosomal function, sensitizes tumors to radiation	Enhances radiation sensitivity	Phase I trials
	Propranolol	Suppresses VEGF and HIF-1α, anti-metastatic effects	Offers anti-metastatic effects and suppresses tumor growth	Retrospective data
	Auranofin	Induces ferroptosis by inhibiting thioredoxin reductase, has immunomodulatory effects	Immunomodulatory effects and ferroptosis in preclinical trials	Phase I trials
Group 4	Valproic Acid	Inhibits HDACs, promotes radiosensitization and differentiation	Improves event-free survival when combined with chemotherapy	Phase II trials
	Metformin	Targets mitochondrial complex I, induces energy stress, activates AMPK	Preclinical evidence supporting use for KDM6A-linked metabolic dysregulation	Preclinical studies
	Hydralazine	Induces DNA demethylation, reactivates PRDM6, reduces chemotherapy resistance	Reduces chemotherapy resistance in preclinical models	Preclinical studies
Pan-subgroup agents	Losartan	Inhibits TGF-β, reduces fibrosis, normalizes tumor vasculature, enhances drug delivery	Enhances drug delivery by normalizing vasculature	Preclinical studies
	Atorvastatin	Blocks RAS/RAF signaling via HMG-CoA inhibition, anti-angiogenic effects	Prevents leptomeningeal spread and anti-angiogenic effects	Preclinical studies
	Disulfiram	Generates ROS through ALDH inhibition, induces copper-dependent apoptosis	Targets hypoxic tumor regions, inducing apoptosis through ROS generation	Preclinical studies

AMPK AMP-activated protein kinase, *HDAC* histone deacetylase, *HIF-1α* hypoxia-inducible factor 1 alpha, *mRNA* messenger RNA, *MYC* myelocytomatosis, *PKCδ* protein kinase C delta, *ROS* reactive oxygen species, *SHH* Sonic Hedgehog, *SMO* smoothened, *VEGF* vascular endothelial growth factor, *WNT* wingless/integrated

hypoxic tumor regions [90]. These agents offer multi-target therapeutic strategies with the potential to enhance treatment effectiveness across MB subtypes (Table 2).

6 Research Gaps and Future Prospects

Medulloblastomas are highly heterogeneous tumors with distinct subgroups (WNT, SHH, Group 3, and Group 4), each defined by unique genetic and epigenetic landscapes. Despite progress in subgroup characterization, the interplay between genetic variants, epigenetic modifications, and tumor behavior remains incompletely understood, limiting the development of effective targeted therapies. Advancing this field will require the identification of subgroup-specific molecular markers to enable precise diagnostics and personalized treatment, alongside deeper investigations into clonal evolution, particularly in high-risk subgroups such as Group 3, to understand mechanisms driving therapy resistance and disease progression.

While current treatments involving surgery, chemotherapy, and radiation have improved survival, they remain constrained by neurotoxicity, recurrence, and resistance, especially in aggressive subtypes. Understanding the mechanisms that contribute to therapy resistance, including DNA repair pathways, epigenetic reprogramming, and the persistence of cancer stem cell populations, will be crucial. Moreover, exploring the role of the TME in supporting immune evasion and treatment resistance may uncover opportunities for therapeutic intervention by targeting the immunesuppressive components of the TME.

Building on these insights into the TME, recent advances in disease modeling have introduced human-induced pluripotent stem cell-derived cerebellar organoids and patient-derived MB organoids, which closely recapitulate tumor heterogeneity, subgroup-specific molecular features, and microenvironmental interactions in vitro [91]. For example, *PTCH1*-mutant cerebellar organoids have been shown to model early MB tumorigenesis, and the MEDB-22 human induced pluripotent stem cell model carrying *ELP1* and *PTCH1* variants enables the study of hereditary SHH-MB predisposition. These organoid systems are increasingly used for high-throughput drug screening, functional genomics, and co-culture experiments, providing a platform to study patient-specific therapeutic responses under conditions that mimic native tumor biology [92]. Importantly, they are now being explored to evaluate immunotherapeutic approaches, including CAR-T therapies, supporting the development of personalized treatment strategies. Incorporating these models into preclinical pipelines has the potential to accelerate drug discovery, guide therapy selection, and reduce reliance on animal models, thereby complementing ongoing efforts to repurpose existing drugs and develop new targeted therapies [93].

Drug repurposing represents a practical strategy for accelerating treatment development in MB by leveraging the safety profiles of existing FDA-approved drugs to target key oncogenic pathways. However, systematic screening to identify effective repurposed drugs remains underexplored, and challenges related to pediatric pharmacokinetics and safe delivery across the BBB must be addressed to facilitate clinical implementation.

The BBB itself poses a significant obstacle to effective drug delivery in MB. Research efforts should focus on developing strategies to enhance BBB penetration, such as utilizing exosomes, liposomal carriers, and nanoparticle-based delivery systems to improve therapeutic concentrations in the brain. Additionally, expanding the use of localized delivery techniques, including intrathecal administration and convection-enhanced delivery, offers the potential to increase drug efficacy within the brain and CSF while minimizing systemic side effects.

The development of advanced targeted therapies and immunotherapies offers hope for improved MB treatment outcomes but is challenged by issues of toxicity, resistance, and immune evasion. Future strategies should emphasize creating subgroup-specific therapies that align with molecular profiles, such as addressing *MYC* amplification in Group 3 or *SMO* variants in SHH tumors, to improve precision and efficacy. In parallel, refining immunotherapies, including CAR-T approaches such as B7-H3-CAR-T and GD2-CAR-T, will require overcoming the barriers posed by tumor heterogeneity and immune escape mechanisms to enhance therapeutic durability.

Epigenetic modifications and non-coding RNAs play critical roles in MB pathogenesis, yet their therapeutic potential remains underutilized. Investigating the roles of long non-coding RNAs, including *MALAT1* and *HOTAIR*, in MB progression may reveal new therapeutic targets, while focusing on key epigenetic regulators, such as *EZH2*, could inform novel treatment strategies, particularly for Group 4 MB, where epigenetic dysregulation is prominent.

Looking forward, the integration of personalized medicine into MB treatment is essential to improving outcomes. This will require the incorporation of comprehensive molecular profiling, including genomic sequencing, transcriptomics, and proteomics, into routine clinical practice to enable accurate patient stratification and targeted therapy selection. Additionally, leveraging AI and machine learning can facilitate the identification of effective drug combinations, predict treatment responses, and tailor treatment regimens to individual patient profiles, thereby advancing precision oncology in MB.

7 Summary

Medulloblastomas are the most common pediatric brain tumors and are classified into four major subgroups—WNT, SHH, Group 3, and Group 4—each with distinct molecular profiles that shape tumor progression and treatment response. Despite advances in understanding MB biology, high-risk subtypes and specific molecular features continue to exhibit poor survival rates and resistance to conventional therapies. In particular, MYC amplification is a key driver of poor outcomes within Group 3, whereas other Group 3 tumors can respond favorably to standard therapy. Although current treatments have improved survival, they often lead to severe long-term side effects, and the BBB limits the effective delivery of many therapies.

Drug repurposing offers a promising strategy to accelerate treatment options by utilizing FDA-approved agents such as niclosamide, itraconazole, and arsenic trioxide to overcome resistance pathways in MB. However, challenges remain, including the need for improved BBB penetration and the lack of pediatric-specific pharmacokinetic data, which hinder effective clinical implementation. Future research should prioritize enhancing drug-delivery systems, investigating synergistic drug combinations, and incorporating personalized medicine approaches guided by comprehensive molecular profiling. Emerging technologies, including nanotechnology-based delivery platforms, CRISPR gene editing, and CAR-T therapies, hold potential to transform MB treatment. Addressing challenges related to toxicity, off-target effects, and the development of reliable biomarkers will be essential to translating these innovations into clinical care. By integrating drug repurposing strategies with targeted therapies and precision medicine, there is potential to improve survival outcomes and quality of life for children with MB.

8 Conclusions

In addressing the challenges MBs present in pediatric oncology, it is evident that innovative, less toxic therapeutic strategies are urgently needed, particularly for high-risk subtypes such as Group 3, where current treatments remain inadequate despite advances in molecular understanding. Drug repurposing, by leveraging FDA-approved agents to target critical pathways in MB, offers a viable and accelerated pathway toward improving treatment outcomes, even as barriers such as effective BBB penetration and pediatric-specific pharmacokinetics require resolution. The path forward in MB treatment will depend on the integration of personalized medicine, where molecular profiling enables the precise tailoring of therapies to each subgroup's unique characteristics. Additionally, emerging technologies, including nanotechnology-based delivery systems, CRISPR gene editing, and CAR-T therapies, hold substantial potential to transform the treatment landscape for MB, provided issues related to safety and biomarker development are addressed. Ultimately, combining drug repurposing with targeted therapies, immunotherapy, and precision medicine represents a strategic direction capable of not only improving survival but also enhancing the quality of life for pediatric patients with MB. Continued commitment to these research avenues will be essential in transforming MB from a devastating diagnosis into a disease that is not only treatable but managed with greater safety, precision, and hope for affected children and their families.

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References

1. Alsaedi MA, Strathdee G. The role of DNA methylation in directing treatment in medulloblastoma. Epigenomics. 2025;1–12. https://doi.org/10.1080/17501911.2025.2554570.
2. Sidaway P. Medulloblastoma: prognostic subtypes revealed. Nat Rev Clin Oncol. 2021;18:131–2.
3. Funakoshi Y, Sugihara Y, Uneda A, Nakashima T, Suzuki H. Recent advances in the molecular understanding of medulloblastoma. Cancer Sci. 2023;114:741–9.
4. Schwalbe EC, Lindsey JC, Danilenko M, Hill RM, Crosier S, Ryan SL, et al. Molecular and clinical heterogeneity within MYC-family amplified medulloblastoma is associated with survival outcomes: a multicenter cohort study. Neuro Oncol. 2025;27:222–36.
5. Kerstens C, Wildiers HP, Schroyen G, Almela M, Mark RE, Lambrecht M, et al. A systematic review on the potential acceleration of neurocognitive aging in older cancer survivors. Cancers. 2023;15:1215.
6. Mitusova K, Peltek OO, Karpov TE, Muslimov AR, Zyuzin MV, Timin AS. Overcoming the blood–brain barrier for the therapy of malignant brain tumor: current status and prospects of drug delivery approaches. J Nanobiotechnol. 2022;20:412.
7. Rechberger JS, Toll SA, Biswas S, You HB, Chow WD, Kendall N, et al. Advances in the repurposing and blood–brain barrier penetrance of drugs in pediatric brain tumors. Cancers. 2025;17:439.
8. Fong D, Christensen CT, Chan MM. Targeting cancer stem cells with repurposed drugs to improve current therapies. Recent Pat Anticancer Drug Discov. 2021;16:136–60.
9. Sursal T, Ronecker JS, Dicpinigaitis AJ, Mohan AL, Tobias ME, Gandhi CD, et al. Molecular stratification of medulloblastoma: clinical outcomes and therapeutic interventions. Anticancer Res. 2022;42(5):2225–39.
10. Suchors C, Kim J. Canonical hedgehog pathway and noncanonical GLI transcription factor activation in cancer. Cells. 2022;11:2523.
11. Stepien N, Senfter D, Furtner J, Haberler C, Dorfer C, Czech T, et al. Proof-of-concept for liquid biopsy disease monitoring of MYC-amplified group 3 medulloblastoma by droplet digital PCR. Cancers. 2023;15:2525.
12. Richardson S, Hill RM, Kui C, Lindsey JC, Grabovksa Y, Keeling C, et al. Emergence and maintenance of actionable genetic drivers at medulloblastoma relapse. Neuro Oncol. 2022;24:153–65.
13. Sokolov D, Sharda N, Banerjee A, Denisenko K, Basalious EB, Shukla H, et al. Differential signaling pathways in medulloblastoma: nano-biomedicine targeting non-coding epigenetics to improve current and future therapeutics. Curr Pharm Des. 2024;30:31–47.
14. Kumar D, Kanchan R, Chaturvedi NK. Targeting protein synthesis pathways in MYC-amplified medulloblastoma. Discov Oncol. 2025;16:23.
15. Sun Y, Xu Z, Wang Z, Zhang Y, Zhang P, Sheng L, et al. KMT2D upregulates SMG1 via histone methylation to antagonize mTOR and reinforce DLBCL ferroptosis. J Leukoc Biol. 2025;117:qiaf092.
16. Kanit N, Uysal Yoca O, Ince D, Olgun N, Ozer E. Gene-specific DNA methylation profiles in pediatric medulloblastomas. Pediatr Dev Pathol. 2022;25:82–90.
17. Westphal MS, Lee E, Schadt EE, Sholler GS, Zhu J. Identification of let-7 miRNA activity as a prognostic biomarker of SHH medulloblastoma. Cancers. 2021;14:139.
18. van Bree NF, Wilhelm M. The tumor microenvironment of medulloblastoma: an intricate multicellular network with therapeutic potential. Cancers. 2022;14(20):5009.
19. Korshunov A, Okonechnikov K, Stichel D, Ryzhova M, Schrimpf D, Sahm F, et al. Integrated molecular analysis of adult sonic hedgehog (SHH)-activated medulloblastomas reveals two clinically relevant tumor subsets with VEGFA as potent prognostic indicator. Neuro Oncol. 2021;23(9):1576–85.
20. Manfreda L, Rampazzo E, Persano L, Viola G, Bortolozzi R. Surviving the hunger games: metabolic reprogramming in medulloblastoma. Biochem Pharmacol. 2023;215:115697.
21. Werbowetski-Ogilvie TE. From sorting to sequencing in the molecular era: the evolution of the cancer stem cell model in medulloblastoma. FEBS J. 2022;289(7):1765–78.
22. Minturn JE, Mochizuki AY, Partap S, Belasco JB, Lange BJ, Li Y, et al. A pilot study of low-dose craniospinal irradiation in patients with newly diagnosed average-risk medulloblastoma. Front Oncol. 2021;11:744739.
23. Banjarnahor CTU, Nainggolan A, Hariyanto AD. Craniospinal irradiation in adult medulloblastoma: a case report and analysis of treatment planning comparing volumetric modulated arc therapy and three-dimensional conformal radiotherapy. Indones J Cancer. 2025;19(2):305–10.
24. Pan Z, Bao J, Wei S. Advancing medulloblastoma therapy: strategies and survival insights. Clin Exp Med. 2025;25(1):119.
25. Dias MV, Isom B, Poole K, Triplett S, Sadanandan N. Evaluating the efficacy of targeted inhibitor therapeutics for Sonic Hedgehog medulloblastoma: significant milestones and current limitations. Georget Sci Res J. 2021;1(1):84–98.
26. Talbot J, Fombonne J, Torrejon J, Babcock BR, McSwain LF, Rama N, et al. Sonic hedgehog medulloblastomas are dependent on Netrin-1 for survival. Nat Commun. 2025;16(1):5137.
27. Whitfield JR, Soucek L. MYC in cancer: from undruggable target to clinical trials. Nat Rev Drug Discov. 2025;24(6):445–57.
28. Ding H, Xu W, Dai M, Li S, Xin W, Tong Y, et al. Hematological toxicity of cyclin-dependent kinase 4/6 inhibitors in patients with breast cancer: a network meta-analysis and pharmacovigilance study. Expert Opin Drug Saf. 2025;24(2):157–65.
29. Yu J, Han J, Yu M, Rui H, Sun A, Li H. EZH2 inhibition sensitizes MYC-high medulloblastoma cancers to PARP inhibition by regulating NUPR1-mediated DNA repair. Oncogene. 2025;44(6):391–405.
30. Ling J, Tang Z, Yang W, Li Y, Dong X. Pygo2 activates BRPF1 via Pygo2–H3K4me2/3 interaction to maintain malignant progression in colon cancer. Exp Cell Res. 2023;431(1):113696.
31. Pećina-Šlaus N, Aničić S, Bukovac A, Kafka A. Wnt signaling inhibitors and their promising role in tumor treatment. Int J Mol Sci. 2023;24(7):6733.
32. Paul MR, Zage PE. Overview and recent advances in the targeting of medulloblastoma cancer stem cells. Expert Rev Anticancer Ther. 2021;21(9):957–74.
33. Desai K, Wanggou S, Luis E, Whetstone H, Yu C, Vanner RJ, et al. Olig2 mediates a rare targetable stem cell fate transition in sonic hedgehog medulloblastoma. Nat Commun. 2025;16(1):1092.
34. Zhang J, Li S, Wang Y, Liu J, Liu Y, Gong X, et al. Tumor-associated macrophages correlate with better outcome in SHH medulloblastoma. Front Oncol. 2025;15:1557313.
35. Gu XY, Yang JL, Lai R, Zhou ZJ, Tang D, Hu L, et al. Impact of lactate on immune cell function in the tumor microenvironment: mechanisms and therapeutic perspectives. Front Immunol. 2025;16:1563303.
36. Timpanaro A, Song EZ, Amwas N, Chiu CH, Ronsley R, Taylor MR, et al. Evolving CAR T-cell therapy to overcome the barriers in treating pediatric central nervous system tumors. Cancer Discov. 2025;15(5):890–902.
37. Bitar L, Schumann U, König R, Zipp F, Schmidt MH. Targeting immune modulators in glioma while avoiding autoimmune conditions. Cancers. 2021;13(14):3524.
38. Ramapriyan R, Sun J, Curry A, Richardson LG, Ramesh T, Gaffey MA, et al. The role of antibody-based therapies in neuro-oncology. Antibodies. 2023;12(4):74.

39. Belgiovine C, Mebelli K, Raffaele A, De Cicco M, Rotella J, Pedrazzoli P, et al. Pediatric solid cancers: dissecting the tumor microenvironment to improve the results of clinical immunotherapy. Int J Mol Sci. 2024;25(6):3225.
40. Toropko M, Chuvpilo S, Karabelsky A. Mirna-mediated mechanisms in the generation of effective and safe oncolytic viruses. Pharmaceutics. 2024;16(8):986.
41. Li S, Poolen GC, van Vliet LC, Schipper JG, Broekhuizen R, Monnikhof M, et al. Pediatric medulloblastoma express immune checkpoint B7–H3. Clin Transl Oncol. 2022;24(6):1204–8.
42. Golubovskaya V. CAR-T cells targeting immune checkpoint pathway players. Front Biosci (Landmark Ed). 2022;27(4):121.
43. Preston H, Casey R, Ferris E, et al. Human cytomegalovirus immune evasion of natural killer cells: a virus for all seasons? Pathogens. 2025;14(7):629. https://doi.org/10.3390/pathogens14070629.
44. Ding L, Kshirsagar P, Agrawal P, Murry DJ. Crossing the blood–brain barrier: innovations in receptor- and transporter-mediated transcytosis strategies. Pharmaceutics. 2025;17(6):706.
45. Jiao Y, Yang L, Wang R, Song G, Fu J, Wang J, et al. Drug delivery across the blood–brain barrier: a new strategy for the treatment of neurological diseases. Pharmaceutics. 2024;16(12):1611.
46. Modi DM, Modi AD. Nanogel-mediated therapeutic delivery across blood–cerebrospinal fluid and blood–spinal cord barriers. Brain Disorders. 2024. https://doi.org/10.1016/j.dscb.2024.100151.
47. Upton DH, Ung C, George SM, Tsoli M, Kavallaris M, Ziegler DS. Challenges and opportunities to penetrate the blood–brain barrier for brain cancer therapy. Theranostics. 2022;12(10):4734.
48. Tarantino S, Bianco A, De Matteis V, Scarpa E, Rinaldi R. Nanotechnology in brain cancer treatment: the role of gold nanoparticles as therapeutic enhancers. ibrain. 2025;11(2):119–45.
49. Abballe L, Spinello Z, Antonacci C, Coppola L, Miele E, Catanzaro G, et al. Nanoparticles for drug and gene delivery in pediatric brain tumors' cancer stem cells: current knowledge and future perspectives. Pharmaceutics. 2023;15(2):505.
50. Yao B, Delaidelli A, Vogel H, Sorensen PH. Pediatric brain tumours: lessons from the immune microenvironment. Curr Oncol. 2023;30(5):5024–46.
51. Liu AP, Smith KS, Kumar R, Paul L, Bihannic L, Lin T, et al. Serial assessment of measurable residual disease in medulloblastoma liquid biopsies. Cancer Cell. 2021;39(11):1519–30.
52. Sun Y, Li M, Ren S, Liu Y, Zhang J, Li S, et al. Exploring genetic alterations in circulating tumor DNA from cerebrospinal fluid of pediatric medulloblastoma. Sci Rep. 2021;11(1):5638.
53. de Santis JO, de Sousa GR, Queiroz RGDP, Cândido MF, Almeida F, de Rezende CP, et al. Immunomodulatory role of exosome-derived content in pediatric medulloblastoma: a molecular subgroup perspective. Hum Cell. 2025;38(2):55.
54. Gabriel N, Balaji K, Jayachandran K, Inkman M, Zhang J, Dahiya S, et al. Loss of H3K27 trimethylation promotes radiotherapy resistance in medulloblastoma and induces an actionable vulnerability to BET inhibition. Cancer Res. 2022;82(10):2019–30.
55. Wang YRJ, Wang P, Yan Z, Zhou Q, Gunturkun F, Li P, et al. Advancing presurgical non-invasive molecular subgroup prediction in medulloblastoma using artificial intelligence and MRI signatures. Cancer Cell. 2024;42(7):1239–57.
56. Karabacak M, Ozkara BB, Ozturk A, Kaya B, Cirak Z, Orak E, et al. Radiomics-based machine learning models for prediction of medulloblastoma subgroups: a systematic review and meta-analysis of the diagnostic test performance. Acta Radiol. 2023;64(5):1994–2003.
57. Zeuner S, Vollmer J, Sigaud R, Oppermann S, Peterziel H, ElHarouni D, et al. Combination drug screen identifies synergistic drug interaction of BCL-XL and class I histone deacetylase inhibitors in MYC-amplified medulloblastoma cells. J Neurooncol. 2024;166(1):99–112.
58. Jensen MP, Qiang Z, Khan DZ, Stoyanov D, Baldeweg SE, Jaunmuktane Z, et al. Artificial intelligence in histopathological image analysis of central nervous system tumours: a systematic review. Neuropathol Appl Neurobiol. 2024;50(3):e12981.
59. Sharif Rahmani E, Lawarde A, Lingasamy P, Moreno SV, Salumets A, Modhukur V. Mbmethpred: a computational framework for the accurate classification of childhood medulloblastoma subgroups using data integration and AI-based approaches. Front Genet. 2023;14:1233657.
60. Tsiami F, Lago C, Pozza N, Piccioni F, Zhao X, Lülsberg F, et al. Genome-wide CRISPR-Cas9 knockout screens identify DNMT1 as a druggable dependency in sonic hedgehog medulloblastoma. Acta Neuropathol Commun. 2024;12(1):125.
61. Maj D, Górka K. Applications of CRISPR/Cas9 technology in mice and livestock genome editing: current research. Ann Anim Sci. 2025;25(2):467–81.
62. Gaál Z. Targeted epigenetic interventions in cancer with an emphasis on pediatric malignancies. Biomolecules. 2022;13(1):61.
63. Lago C, Federico A, Leva G, Mack NL, Schwalm B, Ballabio C, et al. Patient-and xenograft-derived organoids recapitulate pediatric brain tumor features and patient treatments. EMBO Mol Med. 2023;15(12):e18199.
64. Kapplingattu SV, Bhattacharya S, Adlakha YK. Mirnas as major players in brain health and disease: current knowledge and future perspectives. Cell Death Discov. 2025;11(1):7.
65. Wang H, Li J, Du F, Deng H. Cancer stem cells: bridging microenvironmental interactions and clinical therapy. Clin Transl Med. 2025;15(7):e70406.
66. Ogawa H, Yoshida K, Hasegawa S, Wada H, Yasui M, Tahara H. Significance of mouse xenograft tumor model using patient-derived cancer organoids for clinical drug development. Front Oncol. 2025;15:1485886.
67. van Essen MJ, Nicheperovich A, Schuster-Böckler B, Becker EB, Jacob J. Sonic hedgehog medulloblastoma cells in co-culture with cerebellar organoids converge towards in vivo malignant cell states. Neuro-Oncol Adv. 2025;7(1):vdae218.
68. Li Y, Lim C, Dismuke T, Malawsky DS, Oasa S, Bruce ZC, et al. Suppressing recurrence in Sonic Hedgehog subgroup medulloblastoma using the OLIG2 inhibitor CT-179. Nat Commun [Internet]. 2025;16(1):1091. https://doi.org/10.1038/s41467-024-54861-3.
69. Collins VG, Kanodia C, Yahya QB, Liistro M, Kaliaperumal C. 5-aminolevulinic acid (5-ALA) in paediatric brain tumour surgery: a systematic review and exploration of fluorophore alternatives. Childs Nerv Syst. 2025;41(1):1–12.
70. Chen H, Zhang G, Qian Y, Peng Y, Li X, Wang J, et al. Advancements in the application of the intersection of medicine and engineering in cancer research. Cancer Nexus. 2025;1(1):e70003.
71. Faisal SM, Yadav M, Gibson GR, Klinestiver AT, Sorenson RM, Cantor E, et al. Current landscape of preclinical models for pediatric gliomas: clinical implications and future directions. Cancers (Basel). 2025;17(13):2221.
72. Green AL, Minard CG, Liu X, Safgren SL, Pinkney K, Harris L, et al. Phase I trial of selinexor in pediatric recurrent/refractory solid and CNS tumors (ADVL1414): a Children's Oncology Group Phase I Consortium trial. Clin Cancer Res. 2025;31(9):1587–95.
73. Gao J, Zhao Y, Wang Z, Liu F, Chen X, Mo J, et al. Single-cell transcriptomic sequencing identifies subcutaneous patient-derived xenograft recapitulated medulloblastoma. Anim Model Exp Med. 2025;8(3):458–72.
74. De Domenico M, Allegri L, Caldarelli G, d'Andrea V, Di Camillo B, Rocha LM, et al. Challenges and opportunities for digital twins in precision medicine from a complex systems perspective. NPJ Digit Med. 2025;8(1):37.

75. Nadin SB, Cuello-Carrión FD, Cayado-Gutiérrez N, Fanelli MA. Overview of Wnt/β-catenin pathway and DNA damage/repair in cancer. Biology (Basel). 2025;14(2):185.
76. Kumavath R, Paul S, Pavithran H, Paul MK, Ghosh P, Barh D, et al. Emergence of cardiac glycosides as potential drugs: current and future scope for cancer therapeutics. Biomolecules. 2021;11(9):1275.
77. Li CL, Fang ZX, Wu Z, Hou YY, Wu HT, Liu J. Repurposed itraconazole for use in the treatment of malignancies as a promising therapeutic strategy. Biomed Pharmacother. 2022;154:113616.
78. Anwer MS, Abdel-Rasol MA, El-Sayed WM. Emerging therapeutic strategies in glioblastsoma: drug repurposing, mechanisms of resistance, precision medicine, and technological innovations. Clin Exp Med. 2025;25(1):117.
79. Huang W, Hao Z, Mao F, Guo D. Small molecule inhibitors in adult high-grade glioma: from the past to the future. Front Oncol. 2022;12:911876.
80. Wang Y, Wang Z, Li S, Ma J, Dai X, Lu J. Deciphering JAK/STAT signaling pathway: a multifaceted approach to tumorigenesis, progression and therapeutic interventions. Int Immunopharmacol. 2024;131:111846.
81. Mainwaring OJ, Weishaupt H, Zhao M, Rosén G, Borgenvik A, Breinschmid L, et al. ARF suppression by MYC but not MYCN confers increased malignancy of aggressive pediatric brain tumors. Nat Commun. 2023;14(1):1221.
82. Roy A, Bera S, Saso L, Dwarakanath BS. Role of autophagy in tumor response to radiation: implications for improving radiotherapy. Front Oncol. 2022;12:957373.
83. Cavalu S, Saber S, Amer AE, Hamad RS, Abdel-Reheim MA, Elmorsy EA, et al. The multifaceted role of beta-blockers in overcoming cancer progression and drug resistance: extending beyond cardiovascular disorders. FASEB J. 2024;38(13):e23813.
84. Jamali F, Lan K, Daniel P, Petrecca K, Sabri S, Abdulkarim B. Synergistic dual targeting of thioredoxin and glutathione systems irrespective of p53 in glioblastoma stem cells. Antioxidants. 2024;13(10):1201.
85. Holmberg KO, Borgenvik A, Zhao M, Giraud G, Swartling FJ. Drivers underlying metastasis and relapse in medulloblastoma and targeting strategies. Cancers (Basel). 2024;16(9):1752.
86. Roberts CT, Raabe N, Wiegand L, Kadar Shahib A, Rastegar M. Diverse applications of the anti-diabetic drug metformin in treating human disease. Pharmaceuticals (Basel). 2024;17(12):1601.
87. Majchrzak-Celińska A, Warych A, Szoszkiewicz M. Novel approaches to epigenetic therapies: from drug combinations to epigenetic editing. Genes. 2021;12(2):208.
88. Luo Z, Chen CY, Li S. Improving tumor targeting and penetration for nanoparticle-mediated cancer therapy. Small Methods. 2025;9(8):2401860.
89. Zhang W, Xu Y, Fang Y, Li M, Li D, Guo H, et al. Ubiquitination in lipid metabolism reprogramming: implications for pediatric solid tumors. Front Immunol. 2025;16:1554311.
90. Nguyen AL, Facey CO, Boman BM. The significance of aldehyde dehydrogenase 1 in cancers. Int J Mol Sci. 2024;26(1):251.
91. Shayestehfar M, Taherkhani T, Jahandideh P, Hamidieh AA, Faramarzpour M, Memari A. Brain tumors and induced pluripotent stem cell technology: a systematic review of the literature. Ann Med Surg. 2025;87(1):250–64.
92. van Essen MJ, Apsley EJ, Riepsaame J, Xu R, Northcott PA, Cowley SA, et al. PTCH1-mutant human cerebellar organoids exhibit altered neural development and recapitulate early medulloblastoma tumorigenesis. Dis Model Mech. 2024;17(2):dmm050323.
93. Poggi A, Reggiani F, Azevedo H, Raffaghello L, Pereira RC. Medulloblastoma: biology and immunotherapy. Front Immunol. 2025;16:1602930.