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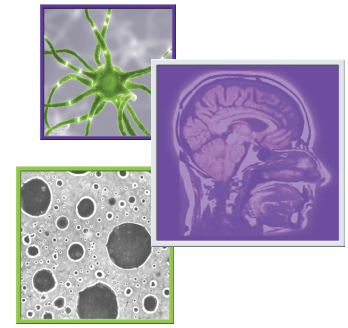
CNS Oncology



Medulloblastoma development: tumor biology informs treatment decisions

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Practice points

- Medulloblastoma is a heterogeneous disease.
- Molecular subgrouping and biology in conjunction with histopathology is increasingly driving prognostication.
- Molecular mechanisms underlying metastatic disease remain to be fully understood.
- Molecular subgrouping provides an opportunity for personalized medicine.
- Combination chemotherapeutic approaches will be important to tackle treatment resistance.
- Immunotherapy may be a novel tool for the treatment of pediatric brain tumors.

SUMMARY Medulloblastoma is the most common malignant pediatric brain tumor. Current treatments including surgery, craniospinal radiation and high-dose chemotherapy have led to improvement in survival. However, the risk for recurrence as well as significant long-term neurocognitive and endocrine sequelae associated with current treatment modalities underscore the urgent need for novel tumor-specific, normal brain-sparing therapies. It has also provided the impetus for research focused on providing a better understanding of medulloblastoma biology. The expectation is that such studies will lead to the identification of new therapeutic targets and eventually to an increase in personalized treatment approaches.

KEYWORDS
• immunotherapy for pediatric brain tumors • medulloblastoma • molecular classification • mouse models and preclinical studies • targeted agents for clinical studies • tumor epigenomics • tumor genomics

Approximately 400–500 new cases of medulloblastoma (MB) are recorded in the USA every year, primarily in children [1]. Current treatment includes surgery followed by radiation and chemotherapy [2,3]. Event-free survival and overall survival vary based on histology: (desmoplastic/nodular MB [DNMB] or MB with extensive nodularity [MBEN], classic MB [CMB] and large-cell/anaplastic [LCA]), extent of resection and presence of metastatic disease at diagnosis. Mortality rates have declined with 60–80% of patients surviving the disease [4,5]. Unfortunately, survivors have poor quality of life associated with disease and therapy-related side effects including long-term physical, endocrine, intellectual and cognitive impairment [6]. Furthermore, these children are at risk for recurrence and secondary malignancies [6]. Children younger than 3 years of age also tend to have worse outcomes [7]. Thus, there is an urgent need to re-evaluate and recalibrate clinical practice

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to limit damage to the developing brain and to improve survival. The research and clinical community have mined human tumor samples to help determine a path forward. As discussed below, studies focused on genetic and epigenetic analyses of patient tumors have shown that MB is not a single disease [8]. This is further complicated by intratumoral heterogeneity, leading to a growing recognition that in place of a uniform therapeutic approach for all MB patients, clinical decisions should take into consideration histopathology and clinical staging in conjunction with knowledge of tumor biology [8,9].

Here, we provide an overview of emerging data from high-throughput analyses of patient tumors, studies on signaling pathways with animal models and efforts to identify novel molecular targets for clinical application. We also discuss the state of newly initiated clinical trials to test molecularly targeted therapies and immunotherapy, and efforts to integrate conventional and novel treatment approaches **(Figure 1)**.

Cerebellar development & MB subtypes

Earliest studies of MB patients suggested a link between perturbations in cerebellar development and genesis of the disease. Familial inheritance accounts for a subset of MBs and is seen in patients with Gorlin's, Turcots and Li-Fraumeni syndrome [10]. Gorlin's syndrome associated with inactivating mutations in the *PTCH-1, -2* and *SUFU* tumor suppressor genes, predisposes to MB development by deregulating the Sonic Hedgehog (Shh) developmental pathway [10]. Turcot's syndrome is characterized by inactivating mutations in the *APC* gene, and results in constitutive activation of the Wingless (Wnt) signaling pathway [10]. Finally, patients with Li–Fraumeni syndrome have germline mutations in the *p53* tumor supressor gene, which predisposes them to various cancers including MB [10]. These observations have led to the generation of the first genetically engineered mice (GEM) models for *Shh* and the *Wnt* driven MBs [11–13]. The animal models in turn have been critical for the identification of the granule neural precursors (GNPs) and the rhombic lip precursors as the cells of origin of Shh and Wnt tumors respectively, the identification of downstream signaling cascade, and finally investigations on targeted therapy.

Sproadic MBs are driven by Shh pathway activation in approximately 20–25% of the cases, while Wnt pathway activation drives approximately 15% of these tumors. Amplifications in *c-MYC* and *N-MYC* occur in 5% of human MBs, while increased expression of gene or protein in the absence of amplification is common in 20–40% of tumors and is associated with poor prognosis [14].

MB genomics

In one of the first application of high-throughput methodologies to pediatric brain tumors, the Pomeroy group showed MBs and atypical teratoid rhabdoid tumors to be distinct disease entities [5]. The disconnect between histological subtyping and outcomes subsequently provided the impetus for international collaborative genome-based studies and efforts to reclassify MBs based on their molecular profile. These genetic and transcriptional profiling studies have led to the identification of four distinct molecular subtypes of MB: WNT/Wingless, SHH/Sonic Hedgehog, Group 3 and Group 4 [14–26]. Whereas WNT subgroup of tumors displayed predominantly CMB histology, SHH tumors included the DNMBs, CMBs and LCA subgroups. Group 3 and 4 tumors present as CMBs or highly aggressive LCAs [14–26]. The molecular classification of MBs in combination with histopathology has also allowed better prediction of likelihood of metastasis. Thus, patients with WNT tumors rarely have metastasis and respond well to therapy, whereas a subset of children with Shh-driven tumors as well as children with high-risk Group 3 and intermediate-risk Group 4 MBs have a significantly increased risk of developing disseminated disease [14–26].

Nevertheless, the same aggressive approach is used to treat all MB patients. SHH, Group 3 and Group 4 patients fail to benefit from the current treatment approaches [3]. Given the better outcomes seen in patients with Wnt-driven tumors, the merits and demerits of treatment de-escalation, specifically craniospinal radiation is being critically debated within the clinical community.

Time for paradigm shift in MB therapeutics?

MB genomics has not only significantly advanced our understanding of tumor biology, but also led to the molecular reclassification of these tumors and set the stage for recalibrating treatment based on specific needs of each patient. We summarize below the hallmarks of the various MB subgroups, preclinical investigations with mouse models and important clinical steps to help improve survival and quality of life.

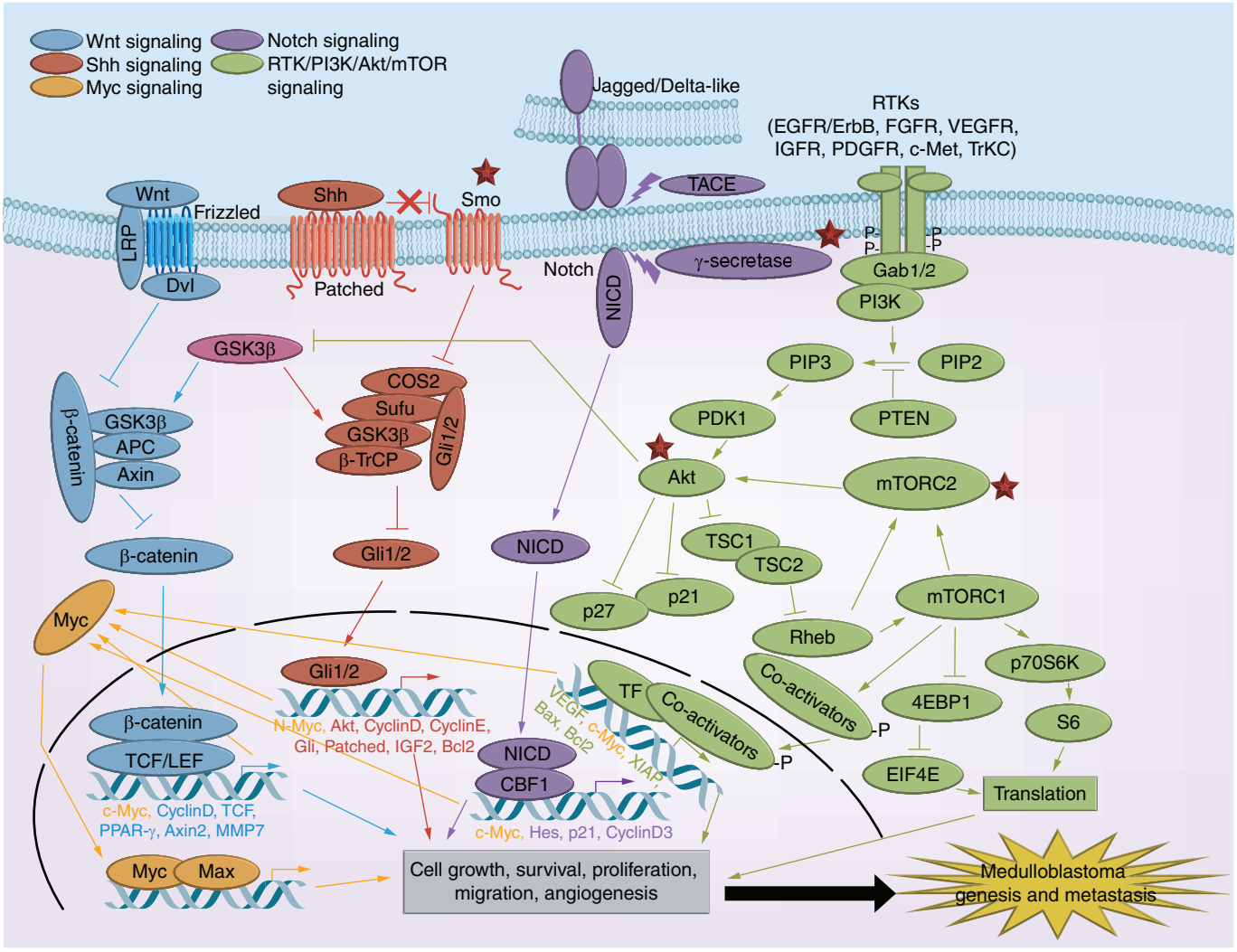

Figure 1. Overview of major signaling pathways and druggable nodels in medulloblastoma. Targets of drugs under clinical investigation in children with pediatric solid/brain tumors are circled.

WNT subgroup

Wnt tumors characterized by constitutive activation of Wnt signaling exhibit mutations in *CTNNB1*, *AXIN1* and *CTNNB1*-associated chromatin re-modelers such as *SMARCA4* and *CREBBP* and epigenetic silencing of genes encoding Wnt signaling antagonists, *SFRP* and *DKK1* [23–29]. Mutations in *p53* are seen in approximately 16% of WNT subgroup tumors [30].

GEM models have definitively shown that constitutive activation of Wnt-β-Catenin signaling in cells of the lower rhombic lip drives development of lesions with proliferating Zic1+ cells [13]. In agreement with data from patient samples, 15% of these mice suffer concurrent deletion of *p53*, resulting in tumors that recapitulate features of human WNT subtype of tumors [13]. These studies also identified genes that maintain this cell lineage (DDX3X), as well as mutated genes that initiate (*CDH1*) or cooperate (*PIK3CA*) in tumorigenesis [13].

Because patients with Wnt tumors have good prognosis and respond well to current standard of care, de-escalation of treatment has been prioritized for clinical evaluation so as to maintain optimum cure rates while aiming for a reduction in side effects [3].

SHH subtype

SHH-subtype MBs are distinguished by constitutive activation of Shh signaling due to loss-of-function mutations in *PTCH1/2* and *SUFU*, gain of function mutations in *SMO* or *GLI-1/2*

amplification, and account for approximately 50% of Shh driven MBs [13–26]. *P53* mutations are seen in a subset of patients with Shh-driven MBs, and portends poor prognosis [30]. These tumors are frequently of the DNMB or MBEN histological subtypes, although a few LCA variants are seen. Indeed, DNMB and MBEN histological subtypes are seen exclusively within the SHH subgroup of MBs. While the prognosis is generally good for patients with Shh-driven tumors, children that present with LCA tumors often have poor prognosis [13–26]. The mechanism(s) underlying this variability are not clear. Mutations in the gene encoding the telomerase reverse transcriptase were seen in approximately 83% of MBs obtained from adult patients, but had an interesting association with good prognosis [31].

GEM models carrying deletion of a copy of the *PTCH1* gene or knock-in of commonly occurring *SMO1* mutations in patients have unequivocally shown that Shh-driven MBs arise from cerebellar GNPs [11,12]. These animal models in conjunction with cell culture systems have unraveled the biology and regulatory network of Shh signaling, providing novel druggable nodes and the basis for numerous preclinical studies. For example, pharmacological inhibition of SMO blocks signal transduction and tumor cell proliferation [32–35]. However, even brief inhibition of Shh signaling in mouse models with the inhibitor HhAntag caused permanent defects in bone development in young mice, precluding further investigations [34]. MBs harboring mutations in *PTCH1* are responsive to SMO inhibitors such as GDC-0449/vismodegib, whereas mutations (in *SUFU*) or amplification (of *MYCN*) of downstream signaling molecules render tumor cells unresponsive to such agents [36,37]. Cholesterol and specific oxysterols are required for Shh pathway signaling, and pharmacological inhibition of their synthesis blocks signal transduction and tumor cell proliferation [38].

Receptor tyrosine kinases including IGF and HGF/c-Met signaling through PI3K are required for Shh-mediated tumorigenesis. PI3K inhibitors, AKT inhibitors, HGF-blocking antibodies alone or in combination with SHH ligand neutralizing antibodies, SMO antagonists and Gas and Survivin inhibitors have all elicited robust response in mouse models [39–45].

Although, the role of Notch signaling in MB genesis has been debated, a recent transcriptome analysis of pediatric MB samples showed that *HES1* overexpression is directly related to shorter survival [46–48]. Although, these analyses were not conducted specifically in the context of Shh-driven tumors, the observations that Notch2 regulates GCP proliferation and that it plays a role in tumor development in SmoA1 mouse models suggest a role for Notch activation in Shh-driven tumors [47,49]. Interestingly, studies with a novel GEM model have shown Shh group of MBs to be generated by activation of Notch signaling in neural stem cells and or in glial cells [50]. If true, pharmacological inhibition of Notch signaling in tumor stem cells or in the tumor microenvironment could be applied for treatment of patients with Shh subgroup of MBs [51]. There is now evidence for negative regulation of Wnt signaling by SUFU, indicating cross-talk between Shh and Wnt signaling pathways as well [52]. These factors will impact the effectiveness of Shh inhibitors in patients and should be considered during trial design.

In one of the first studies to show therapeutic potential of targeting MB metabolism, Gershon and colleagues demonstrated PI3K signaling-dependent induction of aerobic glycolysis in tumors in Smo-M2 mice [53]. Loss of aerobic glycolysis blocked tumor growth and promoted long-term survival in tumor-bearing mice. Shh signaling has been linked to the regulation of the MB epigenome by promoting increased transcription and sustained activation of histone deacetylases (HDACs) leading to increased GNP proliferation [54]. Thus, HDAC inhibitors may have applications in the treatment of Shh-driven MBs.

The variable responsiveness of MBs to chemotherapy and radiation has been attributed to its heterogeneity and the presence of a population of cells called tumor-propagating cells [55]. These cells are often stem cell-like and are marked by the cell surface antigen CD15/SSEA-1. In PTCH mutant mice, $CD15^+$ tumor-propagating cells have dysregulated expression of Aurora kinase and Polo-like kinases (PLK), proteins involved in control of G2-M transit [55]. This vulnerability could be targeted by pharmacological inhibition using the PLK antagonist BI2536, which also enhanced the sensitivity of tumor cells to conventional chemotherapy *in vitro* and *in vivo* [55,56].

PI3K/AKT activation is important in MB dissemination and radio-resistance in mice [57–60]. In preclinical studies, the drugs (PIK-75 and YM024) targeting the p110α catalytic subunit

of PI3K suppressed MB growth [59]. In addition, YM024 and IC87114 (an inhibitor of the p110δ subunit of PI3K) impaired MB cell migration and invasion. The mTORC1 inhibitor RAPA (rapamycin) also suppressed proliferation and migration of MB cells, although the novel mTORC1/2 inhibitor-pp242 appeared to have greater efficacy in inhibiting these processes [59]. Targeting the AKT kinase PDK1 alone with OSU03012 or in combination with the RAPA analog CCI-779 also synergistically blocked AKT activation resulting in potent suppression of MB growth *in vitro* and *in vivo* [59]. Interestingly, an association between elevated expression of the chromatin remodeler, REST, and leptomeningeal disease development was shown in a subset of patients with Shh-driven tumors [61]. A similar observation was made by a separate study, although not necessarily in the context of constitutive Shh activation, which raises the possibility that REST may have a role in driving metastatic disease [62]. REST is associated with a number of druggable activities such as HDAC1/2, the histone methyl transferase-G9a and the histone lysine demethylase LSD1, and REST-high MBs are more sensitive to HDAC inhibitors compared to low-REST isogenic cells [61]. REST also represses the transcription of the anti-proliferative deubiquitylase USP37, and drugs that reactivate *USP37* expression may have therapeutic applications [63].

Preclinical studies directed at understanding therapeutic resistance in Shh-driven MBs have identified mutations in *SMO*, *GLI-2* amplification and activation of PI3K signaling as major contributors to drug resistance [36]. For example, resistance to the SMO inhibitor vismodegib was attributed to *D473H* point mutation in *SMO* [37]. However, resistance to the drug saridegib was independent of the *D473H* mutation and *Gli2* amplification, and was attributed to induction of P-glycoprotein activity [35]. Resistance to the SMO antagonist NVP-LDE225 *in vivo* could be countered by inhibiting PI3K activity using either NVP-BKM120 (a PI3K inhibitor) or NVP-BEZ235 (a dual PI3K and mTOR inhibitor) and mitigated by *PTEN* loss, suggesting that PI3K activation constitutes a mechanism of drug resistance in Shh-driven MBs [64,65].

Group 3

These tumors account for 25% of all MBs and occur more commonly in males and young children, and hardly ever comprise adult patients [13–26]. They frequently encompass the LCA and CMB histologic subtypes, with 50% of the patients exhibiting metastasis at presentation [13–26]. Survival is the lowest in children in this group and is currently at a dismal 20% [13–26].

Recent data suggest that cerebellar GNPs may give rise to Group 3 tumors, although the drivers for this subgroup of tumors are likely to be distinct from constitutive Shh activation [66–68]. Mutations in *p53* that are seen in Shh and Wnt tumor subgroups are absent in subgroup 3 tumors [30]. Gains in chromosome 1q, 7 and 17q and deletions of 10q,11, 16q and 17p are frequently detected, indicating a high level of genomic instability [66–68]. Elevated *c-Myc* expression often with focal amplification of the locus, *PVT1-Myc* fusion, elevated expression of *OTX2*, as well as an increased frequency of mutations in histone H3 lysine (K)-27 demethylases are hallmarks of Group 3 MBs [66–68]. *OTX2* overexpression and knockdown is associated with up- and downregulated expression of several polycomb genes including *EZH2*, *EED*, *SUZ12* and *RBBP4* and genes encoding H3K27 demethylases: KDM6A, KDM6B, JARID2 and KDM7A [66,69]. A novel genetically engineered mouse model with constitutive *OTX2* expression in the postnatal hind-brain showed accumulation of clusters of proliferative cells originating from neural progenitors of the rhombic lip (dorsal brain stem) and migrating GNPs in cerebellar white matter [70]. *OTX2* knockdown in human MB cells increased survival of tumor-bearing mice, indicating that *OTX2* is necessary for tumor maintenance [71]. Studies such as these not only provide insights into mechanisms by which chromatin remodeling is involved in tumor development, but also provide a new class of drug targets. For example, the OTX2 target-*EZH2* can be pharmacologically manipulated by GS2816126, an agent under clinical investigation for adult patients with hematological malignancies [72].

A novel mouse xenograft model (HD-MB03) established from a patient tumor with molecular features Group 3 MBs including isochromosome 17q and *MYC* amplification revealed strong expression of a number of HDACs, including *HDAC-2*, *-5*, *-8* and *-9* [73]. Consistent with these findings, HD-MB03 cells displayed increased sensitivity to the HDAC inhibitors, vorinostat and panobinostat [73]. These inhibitors also conferred increased radiation sensitivity to HD-MB03 cells, providing support for

the use of HDAC inhibitors for the treatment of patients with Group 3 MBs [73].

Molecules that contribute to leptomeningeal disease development in Group 3 tumors are understudied [74,75]. Myc is a prime candidate because of its known roles in regulating migration, invasion and angiogenesis, processes critical to tumor metastasis. Myc inhibition for cancer therapy has been investigated over the years with little success. Nevertheless, agents that target Myc such as S2T1–6OTD, a telomestatin derivative that can bind to the c-Myc promoter, as well as agents that can modulate Myc expression including all-*trans*-retinoic acid (ATRA), the quassinoid analog NBT-272, the anticonvulsant and HDAC inhibitor-valproic acid (VPA), the polyphenol resveratrol, have shown efficacy *in vitro* and in mice, and their further investigation in MYC-high MBs may be warranted [76,77]. The availability of three separate Myc-driven mouse models of LCA MB should further aid in such preclinical studies [78–81].

Immunotherapy is being increasingly viewed as a weapon for use in combination therapy or as an alternative to conventional treatments [82–85]. The ability of immune cells to traffic also increases their attractiveness for treatment of metastatic disease. However, MBs appear to be immunosuppressive in comparison to other pediatric brain tumors and have fewer infiltrating immune cells, which are dominated by immunosuppressive M2 macrophages, $CD8^+$ and $CD4^+$ T cells [86]. The elevated expression of the nonclassical MHC *CD1d* gene, which encodes a receptor for a class of cytotoxic T cells, was recently leveraged to show tumor regression in an Shh mouse model and could be an attractive option for other metastatic MB subgroups as well [87]. The application of T cells for MB treatment could however be hampered by the low expression of HLA-I in neural tumors. The use of chimeric antigen receptor (CAR)-T cells avoids this problem and the use of CAR-T cells specific for HER2 showed efficacy against MB in a murine model [88]. The requirement for tumor-associated antigens (TAAs) can also be circumvented by harnessing the power of components of the innate immune system, such as natural killer (NK) cells [89–91]. NK cells have been tested successfully in cell culture systems [89–91].

Because B-cell function appears to be unaffected in MB patients, antibodies specific for a few TAAs can be evaluated alone or in conjunction with radiation or chemotherapy [92]. SHH and HGF blocking antibodies have been studied for efficacy in murine xenograft models [41]. Finally, antibodies against immunosuppressive molecules or drugs such as HDAC inhibitors that can increase tumor immunogenicity and alter the sensitivity of MBs to immune cells appear attractive for MB treatment [93].

Group 4

Group 4 tumors occur more frequently in older children and accounts for 35% of all MBs. Tumors are frequently of CMB histology with a few instances of LCA [23–29]. Metastasis is observed in 33% of these cases at diagnosis [23–29]. Mutations in p53 have not been described [30]. These tumors exhibit a neuronal molecular signature and exhibit elevated expression of *OTX2*, *N-Myc*, *FST* and *CDK6* [13–26]. Isochromosome 17q and deletion of 17p is a common occurrence [13–26]. Children with Group 4 tumors have an intermediate prognosis [13–26]. Group 4 tumors in adult patients have a particularly poor prognosis [13–26]. Although, these MBs are the most commonly occurring tumors, their biology is the least understood.

N-Myc expression is elevated in human Group 4 MBs and its overexpression driven by the hindbrain specific *Glt-2* promoter in postnatal neural stem cells resulted in non-Shh dependent, disseminated tumors with classic and LCA histology. Metastatic disease development combined with elevated N-Myc and their non-Shh signature suggest that these tumors may resemble human subgroup 4 MBs [79].

Bmi-1 is a polycomb group repressor complex gene overexpressed across all MB subgroups but most significantly in Group 4 tumors and is associated with deregulation of cell adhesion molecules. *In vitro* assays identified Bmi-1 dependent perturbation of cell adhesion and motility through repression of bone morphogenetic proteins (BMPs) [94]. *In vivo*, Bmi-1 controlled invasion in a novel xenograft model of human MB [94]. Thus, BMP agonists may have potential application in the treatment of Group 4 MBs [94].

Tumor biology drives novel clinical trials

Despite considerable preclinical data for targeted therapy, only few agents have been investigated as single agents or in combination with standard of care drugs in pediatric clinical trials. The SMO inhibitor GDC-0449/

vismodegib was recently evaluated in a Phase I clinical trial (NCT00822458) involving children with refractory or relapsed MB [95–98]. The drug was well tolerated with a recommended Phase II dose of 150 or 300 mg. Two dose-limiting toxicities were observed [98]. A partial response was seen in a participant with metastatic MB [98]. It is under active evaluation in combination with temozolomide in a Phase I/II study in children (NCT01878617) and adults (NCT01601184) with MB. NVP-LDE225 (sonidegib) is another SMO inhibitor under clinical investigation as monotherapy in pediatric and adult MB patients (NCT01125800) [99]. It was well tolerated and response was observed in a few patients [98]. A Phase I study of sonidegib in combination with buparlisib (PI3K inhibitor) in adults with advanced solid tumors is ongoing (NCT01576666). The AKT inhibitor MK-2206 was evaluated in a Phase I/II trial of pediatric patients with refractory solid tumors (NCT01231919); study results remain to be released. mTOR inhibitors have been scrutinized in a number of trials for pediatric solid tumors. In a Phase I study, the drug everolimusin was well tolerated with a maximum tolerated dose (MTD) of 5 mg/m^2 [100]. deforolimus, another mTOR inhibitor, was well tolerated in a Phase I trial of pediatric patients with advanced cancers, with one partial response several instances of stable disease [101]. The Phase I study of a third mTOR inhibitor, temsirolimus, revealed safety. However, an MTD was not obtained, and the drug failed to meet criteria for its use as a single agent [102]. Temsirolimus has also been paired with irinotecan and temozolomide (NCT01141244, COG-ADVL0918) in a completed Phase I study for young patients with relapsed or refractory solid tumors; study results have not been posted. The most recent mTOR inhibitor under evaluation in a Phase I trial is ridaforolimus, both alone (NCT01431534) and in combination with dalotuzumab (NCT01431547). Results of these studies have not been posted. A Phase I (NCT01670175) studying the combination of rapamycin (sirolimus), cyclophosphamide and topotecan, in pediatric and young adults with relapsed and refractory solid tumors is currently open. sirolimus was previously studied in combination with vinblastine (NCT01135563); no results have been published to date.

The Notch pathway is known to be important for maintenance of tumor stem cells, a population believed to contribute to treatment resistance [103]. Notch inhibition by the agent MK-0752 was evaluated in a recently completed Phase I trial of pediatric patients with recurrent CNS tumors [103]. Though safety was demonstrated efficacy was modest, thus undermining its use in future trials [103].

HDAC inhibitors have been investigated in two separate Phase I trials in pediatric patients with relapsed/refractory CNS tumors. The HDAC inhibitor vorinostat was well tolerated when combined with either temozolomide or bortezomib (NCT01076530, NCT00994500) [104,105]. The combination of vorinostat, isotretinoin and chemotherapy is under investigation in young patients with embryonal tumor (NCT00867178).

Immunotherapy has been gaining ground as a therapeutic approach for CNS malignancies. The intrathecal infusion of lymphocyte-activated killer (LAK) cells from allogeneic donors in a cohort of six patients with disseminated MB showed some success with three patients displaying no disease or neurological toxicity following treatment [106]. One other case report also echoed this success, warranting further investigation of LAK cells for pediatric CNS tumors [107]. A novel clinical trial investigating the safety and feasibility of fourth ventricular infusion of *ex vivo* expanded and activated NK cells has recently received US FDA approval and is anticipated to begin accruing pediatric patients with recurrent/refractory tumors of the posterior fossa.

^{131}I conjugated GD2 antibodies have been evaluated for the treatment of MB, although a major drawback has been neuropathy associated with the use of GD2 as a target [108]. The use of high-dose chemotherapy followed by autologous stem cell transplant currently being pursued in multiple clinical trials holds promise, and has been attributed to the 'resetting' of the immune system [109]. However, the high relapse rates underscore the need for new combinations to augment the host antitumor immune response.

Conclusion & future perspective

The above discussion has provided a panoramic view of the preclinical studies that have examined the feasibility of targeting MBs. Of these, a few novel agents targeting Shh signaling and PI3K pathway have been explored in Phase I clinical trials in children **(Figure 1)**. At present, very few have been studied in Phase II/III trials.

Trial designs should take into consideration inter- and intratumoral heterogeneity in MBs, and also leverage high-throughput genomics and epigenomics to arrive at a panel of biomarkers that will help predict patient response to therapeutics.

Financial & competing interests disclosure

Work in V Gopalakrishnan's laboratory is supported by grants from the NIH (R01NS079715 and R03NS077021), American Cancer Society (118165-RSG-09-273-01-DDC), Addis Faith, Noah's Light, Rally Vs Cancer, Hyundai Hope on Wheels and The Cure Starts Now Foundations. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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