SciMedCentral

JSM Brain Science

Mini Review

Targeting SHH-Subgroup Medulloblastoma

Kelly Drozdowicz[1], Jun Long[1], Emily Winterbottom[1], David J. Robbins[1,2], Jezabel Rodriguez-Blanco[1]*

[1]The DeWitt Daughtry Family Department of Surgery, University of Miami, USA
[2]Sylvester Comprehensive Cancer Center, University of Miami, USA

*Corresponding author
Jezabel Rodriguez-Blanco, PhD, Molecular Oncology Program, The DeWitt Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Avenue, Miami, FL 33136, USA, Tel: 305-243-5717; Email: jbrodriguez@miami.edu

Submitted: 17 March 2017
Accepted: 16 August 2017
Published: 18 August 2017
Copyright
© 2017 Rodriguez-Blanco et al.
ISSN: 2573-1289

OPEN ACCESS

Keywords
• Medulloblastoma
• HEDGEHOG
• Targeted therapy
• Medulloblastoma treatment

Abstract

Medulloblastoma (MB) is the most common malignant brain tumor in children. While most patients with MB can be cured, current treatments often require broad base therapies, such as radiation and chemotherapy, which can have devastating and long-term effects. Molecular classification of MB into distinct subgroups (WNT, SONIC HEDGEHOG (SHH), Group 3, and Group 4) has provided a template with which to identify and better target these specific tumor subtypes. Aberrant activation of the HEDGEHOG (HH) pathway is implicated in a third of all MB cases, and small-molecule inhibitors have already been developed that target these tumors. Many of such inhibitors specifically target the transmembrane protein SMOOTHENED (SMO), a key rate-limiting step of the HH pathway. Although SMO inhibitors have proven successful in preclinical studies and clinical trials are still ongoing, various mechanisms of treatment resistance have emerged despite initial favorable response. In this review, we focus on the SHH-subgroup MB and discuss recent advances in its clinical management.

ABBREVIATIONS

APC: Adenomatous Polyposis Coli; ATO: Arsenic Trioxide; BCC: Basal Cell Carcinoma; BET: Bromodomain And Extra-Terminal; CSF: Cerebrospinal Fluid; FDA: Federal Drug Administration; GLI-R: GLI truncated Repressor form; HAT: Histone Acetyltransferase; HH: HEDGEHOG; IDH1: Isocitrate Dehydrogenase 1; MAPK: Ras/Mitogen-Activated Protein Kinase; MB: Medulloblastoma; PATCHED1: PTCH1; PI3K: Phosphoinositide 3-Kinase; PKA: Protein Kinase A; PTEN: Phosphatase and Tensin Homolog; SHH-MB: Sonic HEDGEHOG Medulloblastoma; SMO: SMOOTHENED; SUFU: SUPPRESSOR OF FUSED; TERT: TELOMERASE REVERSE TRANSCRIPTASE; TRP53: TRANSFORMATION RELATED PROTEIN 53; YAP1: Yes Associated Protein 1 (YAP1)

INTRODUCTION

Medulloblastoma (MB) is the most common malignant brain tumor in children, accounting for 15-20% of all pediatric brain tumors [1]. The American Cancer Society estimates that between 250 and 500 children are diagnosed with MB each year in the United States [2]. Adult MB is much less common and accounts for only 25-30% of all MB cases [3]. MB starts in the cerebellum, the part of the brain that controls balance, coordination, and other complex motor functions, and can spread to other parts of the brain and spinal cord through the cerebrospinal fluid (CSF). These tumors are fast growing and frequently compress (or grow into) the fourth ventricle, impeding normal CSF flow and causing hydrocephalus [4]. As a result, most patients present with symptoms of increased intracranial pressure such as headaches, nausea, and vomiting. In infants and children, symptoms may also include walking and visual problems, tilted head, neck stiffness, and fontanelle bulging [5].

The exact cause of MB is unknown and most cases are sporadic; however, there are a few rare genetic syndromes that have been linked to increased risk of developing this type of cancer, such as Gorlin, Turcot, and Li-Fraumeni syndrome [6]. Most Gorlin syndrome patients harbor mutations in the tumor suppressor gene *PATCHED1* (*PTCH1*), a key regulator of the HEDGEHOG (HH) pathway. Patients with this syndrome develop multiple basal cell skin cancers (BCC) throughout their lifetime and have an increased risk of developing MB [7,8]. Turcot syndrome patients harbor mutations in a different tumor suppressor gene called *ADENOMATOUS POLYPOSIS COLI* or *APC*. APC is an essential negative regulator in the WNT signaling pathway and mutations have been shown to increase the risk of developing colorectal cancer as well as MB [9]. Patients with Li-Fraumeni syndrome have mutations in the gene that codifies for the TRANSFORMATION RELATED PROTEIN 53 (TRP53 or P53), which predisposes them to several different types of cancer including MB [10]. These heritable syndromes have helped to uncover some of the pathways involved in MB development and highlight the fact that not all MB tumors are driven by the same mutations and thus should not be considered as one uniform malignancy.

CURRENT TREATMENTS

In treating MB, the first step is almost always surgery, the goal being to remove as much of the tumor as possible [11].

This is especially crucial, as multiple studies have shown that survival depends on how much of the tumor is left after resection [12,13]. Surgery is usually followed by radiation to the brain and spinal cord, combined or not with chemotherapy, and followed by several months of chemotherapy [14]. The use of radiation in young children is controversial, and some physicians choose to treat the tumor in another way or restrict radiation to only one part of the brain [4,15]. The treatment regimen varies according to the risk classification of the tumor patient. Average risk patients (older than 3 years, residual tumor after resection smaller than 1.5 cm^2 and/or no metastasis) are treated with radiation with or without vincristine, followed by adjuvant chemotherapy including vincristine, cisplatin, cyclophosphamide and/or lomustine. For high risk patients (younger than 3 years old, with residual tumor bigger than 1.5 cm^2 and/or metastasis) radiation is given at higher dose and is followed by cisplatin, cyclophosphamide and vincristine chemotherapy [16,17]. While most patients with MB can be cured, the cost in terms of long-term side effects can be very high [18]. One of the most common side effects is posterior fossa or cerebellar mutism syndrome; this is a postoperative complication related to disruption of the cerebellar vermis or dentate nuclei [19]. Moreover, younger patients are especially vulnerable to radiation and may develop neurocognitive impairments, hearing loss, growth failure, endocrine abnormalities, cataracts, fertility problems and/or cerebrovascular disease as a result of exposure [20-23]. In addition, radiation and chemotherapy increase the risk of developing secondary cancers or malignancies later on [24-26]. Physicians are working towards reducing these long-term effects, either by limiting the amount of radiation, using proton beams for example [27], offering stem cell transplantion prior to radiation [17] or making use of more targeted drugs with less toxicity. However, in spite of these drawbacks, surgery followed by radiotherapy/chemotherapy remain the standard of care for MB patients [28]. As it stands, current therapies are unlikely to significantly improve MB survival rates, as recurrent disease remains common with such therapies. Recurrent MB is almost uniformly fatal, with less than a 10% chance of survival after radiation [29]. Radiation and cytotoxic chemotherapy unintentionally select for treatment resistant cells, and these escapers drive leptomeningeal dissemination of metastatic clones [30]. For this reason, metastatic tumors have much more in common with each other than to the primary tumors from which they originally came [31].

MOLECULAR CLASSIFICATION

In patients with MB, prognosis depends heavily on the molecular makeup of the tumor [32]. Traditionally, classification schemes were based primarily on histopathology: classic vs. desmoplastic/nodular vs. extensive nodularity vs. large-cell/anaplastic. However, over the last decade, new genomic approaches have enabled the WHO classification of MB into four molecular subgroups based on differences in their transcriptome: WNT, SHH, Group 3, and Group 4 [33,34]. In addition, these molecular subgroups seem to be better predictors of patient outcome [35]. WNT subgroup patients have the best long-term prognosis, with 90% of patients surviving past five years, while Group 3 subgroup patients, which frequently harbor *MYC* amplifications, have the worst prognosis. The SHH subgroup is the most common in infants and adults overall, representing a third of all MB cases [36]. More recently, genome-wide DNA methylation and gene expression analyses have further stratified MB classification, identifying 12 distinct MB subtypes that are both biologically and clinically relevant: two WNT, four SHH, three Group 3, and three Group 4 [37]. Scientists have been able to take advantage of these stratified classifications by developing subgroup specific small-molecule inhibitors, with those targeting the HH pathway among some of the most advanced.

SHH-SUBGROUP MB

SHH-subgroup MB (SHH-MB) was named after the signaling pathway thought to drive tumor formation in that particular subgroup: the HH signaling pathway. HH proteins are powerful signaling molecules that act as morphogens, mitogens, and survival factors depending on the context. In vertebrates, there are three HH ligands: SONIC, DESERT, and INDIAN HEDGEHOG [38]. These are synthesized as precursor proteins and then doubly lipid-modified before being secreted from the cell [39]. SHH signaling in vertebrates (Figure 1) depends on the primary cilium, an antenna-like organelle that extends from the surface of almost every cell type [40]. The primary cilium functions as a focal point for enrichment of SHH signal transduction, with various signaling components trafficking through the primary cilium in a microtubule dependent manner [39]. HH signaling begins when a HH ligand binds to the transmembrane receptor PTCH1 at the base of the primary cilium. This binding releases PTCH1-mediated inhibition of SMO, a G-protein-coupled transmembrane protein [41]. Once activated, SMO is trafficked to the tip of the cilium and binds to SUPPRESSOR OF FUSED (SUFU), relieving its repression of the GLI family of transcription factors. Activated GLI can then translocate to the nucleus and promote expression of downstream targets, such as *GLI1*, *PTCH1*, *CCND1*, and *MYCN* [42]. In the absence of HH ligand, PTCH1 prevents SMO from moving into the cilium, and SUFU targets GLI for proteosomal cleavage. This leads to the conversion of full-length GLI proteins into truncated repressors, GLI-R. GLI-R can then enter the nucleus and inhibit transcription of HH target genes [43-45].

During normal cerebellar development, SHH signaling stimulates the division of cells in the outermost layer of the cerebellum, also known as the external granular layer, and ultimately dictates the size and pattern of the organ [46,47]. In SHH-MB, this pathway is permanently turned on and the cells keep growing and dividing. SHH-driven tumors frequently possess mutations or amplifications in *PTCH1*, *SMO*, *SUFU*, and/or *GLI2*, all key regulators of the HH pathway. Further, SHH-MB can be further classified into three subtypes based on age group: infant (0-3 years), childhood (3-16 years), and adult (>16 years). *PTCH1* mutations are found in more or less equal frequencies across all age groups. In contrast, *SUFU* mutations are found predominantly in infants; *SMO* mutations are found predominantly in adults [48]; and *TRP53* mutations, a poor prognostic indicator [49], are found more frequently in children [48]. Next generation sequencing studies of larger cohorts have also revealed the existence of certain genetic events specific to the SHH subgroup that go beyond the canonical HH pathway, some of which include *ISOCITRATE DEHYDROGENASE 1* (*IDH1)* mutations, somatic alterations that affect histone acetyltransferase

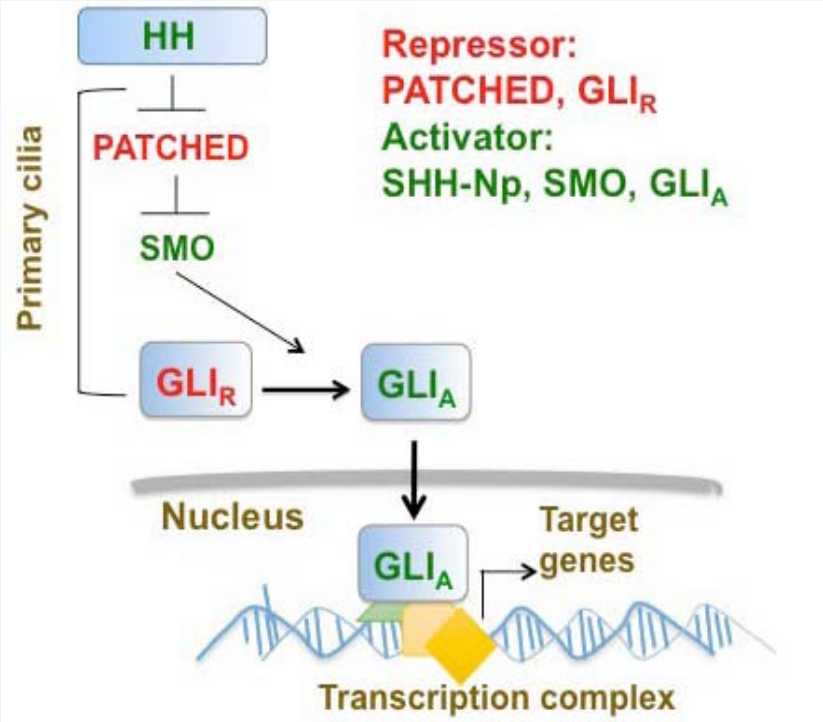

Figure 1 Overview of Hedgehog Signaling. In the presence of HH ligand, PTCH1 releases its inhibition on SMO, which can then move into the cilium and bind to SUFU. This binding relieves repression of GLI, promoting expression of various HH target genes. In the absence of HH ligand, PTCH1 prevents SMO from moving into the cilium, and SUFU targets GLI for proteasomal cleavage, leading to the formation of GLI-R, a transcriptional repressor.

(HAT) complexes [50], *PHOSPHATASE AND TENSIN HOMOLOG* (*PTEN*) loss, *TELOMERASE REVERSE TRANSCRIPTASE* (*TERT*) promoter mutations, and/or *YES ASSOCIATED PROTEIN 1 (YAP1)* amplifications [37]. These findings suggest that in order for SHH-MB treatments to be effective they should target the SHH pathway in a manner consistent with the genetics behind each tumor.

TARGETED THERAPIES

The first identified inhibitor of HH signaling was Cyclopamine, a naturally occurring chemical that was discovered after causing birth defects in sheep [51]. Although it failed to translate clinically, Cyclopamine sparked the idea of using HH pathway inhibitors in cancer. Today, numerous HH inhibitors have been developed and many are undergoing clinical trials for a broad spectrum of HH-driven tumors (Table 1). The majority of these inhibitors target SMO, a key rate-limiting component of the HH pathway, and a few have also been evaluated in MB clinical trials, such as Vismodegib (GDC-0449) and Sonidegib (LDE-225) [52] (Table 2). Of these, Vismodegib became the first to receive FDA approval for advanced basal BCC patients [53], and clinical trials are already underway for other HH-driven malignancies, including several phase I and II trials for SHH-MB patients.

Vismodegib has garnered a lot of excitement as the first SMO antagonist to receive FDA approval, and while there have been favorable responses recorded; these are usually only transient, with tumor regrowth and metastasis commonly observed [52]. In a pioneering case study, treatment with Vismodegib in an adult patient with metastatic SHH-MB resulted in rapid tumor regression, decreased reported pain, and notable weight gain [54]. However, despite this promising response, the patient quickly relapsed after just three months of treatment. Further analysis of the tumor specimen before and after treatment revealed that it had acquired a secondary mutation in SMO that likely drove treatment resistance [55]. Since this study, a variety of other HH inhibitors have been investigated in the clinic, but SMO antagonists remain the most popular mode of intervention. In a related study, Vismodegib showed efficacy against adult recurrent SHH-MB with longer progression-free survival when compared with non-SHH-MB patients. However, among those with SHH-MB, prolonged disease stabilization occurred in only 41% of patient cases [56,57]. Interestingly, a recent genomic profiling study of SHH-MB patients identified mutations in *SUFU*, *GLI2*, and *MYCN* as drivers of primary resistance to SMO inhibitors [48]. Furthermore, genomic analyses of relapsed BCC tumors also showed that resistance to Vismodegib is associated with HH pathway reactivation via mutations in *SMO* that prevent drug binding and/or *SUFU* or *GLI2* amplifications [58].

Primary and acquired resistance to Vismodegib stress the need for novel targeted therapies. In turn, a number of molecules that target the HH pathway at distinct sites are currently being evaluated. Itraconazole and Saridegib (IPI-926) have shown great promise in pre-clinical MB models [59,60], including those resistant to Vismodegib [61], by binding to a different pocket on SMO. In addition, these compounds have already been assayed in clinical trials for BCC, prostate cancer, and advanced pancreatic adenoma among others [62]. The use of inhibitors that target the GLI family of transcription factors have also shown potential [63,64]. In particular, arsenic trioxide (ATO) has exhibited efficacy

Table 1: 2017 clinical trials running for SHH inhibitors. Status as of April 2017.

Compound	Target	Type of Malignancy
Vismodegib (GDC-0449)	SMO	Basal Cell Carcinoma Recurrent Medulloblastoma Basal Cell Nevus Syndrome Castration-Resistant Prostate Cancer Myelofibrosis Chondrosarcoma Advanced Pancreatic Cancer Metastatic Gastric & Esophageal Cancer Small-Cell Lung Cancer Acute Myeloid Leukemia
Sonidegib (LDE-225)	SMO	Recurrent and Relapsed Medulloblastoma Prostate Cancer Castration-Resistant Prostate Cancer Pancreatic Adenocarcinoma Advanced Pancreatic Cancer Refractory Multiple Myeloma Recurrent Ovarian Cancer Triple-Negative Breast Cancer
BMS-8339233 (XL139)	SMO	Basal Cell Nevus Syndrome Leukemia Small Cell Lung Carcinoma Esophageal Neoplasms Stomach Neoplasms
Glasdegib (PF-04449913)	SMO	Myelodysplastic Syndrome Acute Myeloid Leukemia Primary Myelofibrosis Myelodysplastic Syndrome Acute Lymphoblastic Leukemia Chronic Myelomonocytic Leukemia
Saridegib (IPI-926)	SMO	Primary Myelofibrosis Basal Cell Carcinoma/Chondrosarcoma Metastatic Pancreatic Cancer Recurrent Head and Neck Cancer Conventional Chondrosarcoma
Taladegib (LY2940680)	SMO	Esophageal Cancer Advanced or Metastatic Solid Tumors
Arsenic Trioxide (ATO)	GLI	Non-small Cell Lung Cancer Recurrent Urethral Cancer Basal Cell Carcinoma Malignant Glioma Myelodysplastic Syndromes Multiple Myeloma Advanced Neuroblastoma Chronic Myelogenous Leukemia Pancreatic Cancer Breast Cancer Liver Cancer Kidney Cancer Cervical Cancer Lymphoma Prostate Cancer Leukemia Acute Promyelocytic Leukemia
I-BET762 (GSK 525762A)	GLI/MYC	Relapsed, Refractory Hematologic Malignancies Estrogen Receptor Positive Breast Cancer NUT Midline Carcinoma

Abbreviations: SMO: SMOOTHENED

against SHH-MB resistant to SMO inhibitors [61]. Moreover, ATO has already received FDA approval for treatment of acute promyelocytic leukemia [65], and numerous clinical trials are still ongoing (Table 1). Other promising GLI inhibitors include GANT58 and GANT61. These compounds function by inhibiting GLI DNA binding [66], but despite encouraging preclinical studies in MB [67] and other solid tumors [68,69], they have yet to be tested in the clinic. CASEIN KINASE-1α agonists, such as Pyrvinium, have also been shown to reduce the stability of GLI proteins. Pyrvinium in particular has shown efficacy in Vismodegib resistant scenarios as well as inhibiting SHH-driven tumors [70]. Recently, inhibition of bromodomain and extra-terminal (BET) proteins and epigenetic signaling has gained attention as a potential new direction for treatment of GLI-dependent cancers, including MB [71,72]. I-BET762 (GSK525762), an epigenetic reader domain inhibitor, is currently undergoing clinical trials for various hematologic malignancies and solid tumors [73]. Lastly, recent studies have shown that modulation of alternative signaling pathways, such as PHOSPHOINOSITIDE 3-KINASE (PI3K) [74], RAS/MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) [75], and PROTEIN KINASE A (PKA) [76], may actually prevent or overcome resistance to SMO inhibitors. Excitingly, combinations of SMO and PI3K inhibitors are already being clinically assayed for advanced solid tumors (NCT01576666), and are likely to benefit those SHH-MB patients with activated PI3K signaling [48].

While targeted therapies for MB show great promise in addressing the root cause or causes of malignancy, there are issues with how these therapies are actually being utilized. Single-tumor biopsies only reveal a small portion of the genetic aberrations present in an entire tumor, and current studies show that even though MB has spatially homogenous transcriptomes, thereby allowing its molecular classification, somatic mutations within these tumors are spatially heterogeneous. Thus this intratumoral heterogeneity creates an additional challenge to using any particular targeted-therapy [77,78].

CONCLUSIONS

Improved therapies for pediatric brain tumor patients has significantly increased their five-year survival. Still, morbidity associated with surgery, radiation and chemotherapy remains a major concern when dealing with pediatric cancer. The use of targeted therapies to increase efficacy and reduce non-specific secondary effects is an appealing prospect. However, the emergence of primary and secondary drug resistance to such targeted therapies highlights the clinical challenges of using these new treatment modalities.

ACKNOWLEDGEMENTS

We would like to thank members of the Robbins and Capobianco laboratories for providing their insights during discussions regarding this manuscript.

FUNDING

Childhood Brain Tumor Foundation (JRB), FICYT POST10-27 (JRB), Alex Lemonade Stand Foundation M1201547 (DJR), 1R21NS096502-01 (DJR). The University of Miami Women's

Table 2: 2017 clinical trials running for medulloblastoma patients. Status as of April 2017.

Compound	Target	Phase	Participant Population
Vismodegib	SMO	I/II	Adult patients with recurrent, progressive, or refractory MB (NCT01601184)
(GDC-0449)		II	Children with newly diagnosed MB (NCT01878617)
		II	Adult patients with recurrent or refractory MB (NCT00939484)
		II	Children with recurrent or refractory MB (NCT01239316)
		I	Children with recurrent or refractory MB (NCT00822458)
		I	Patients with locally advanced or metastatic solid tumors (NCT00607724)
Sonidegib	SMO	II	Patients with HH-pathway activated relapsed MB (NCT01708174)
(LDE-225)		I/II	Children with recurrent or refractory MB, or other tumors potentially dependent on HH signaling pathway (NCT01125800)
		I	East Asian with advanced solid tumors (NCT01208831)
		I	Patients with advanced solid tumors (NCT00880308)

Abbreviations: HH: HEDGEHOG; MB: medulloblastoma; SMO: SMOOTHENED

Cancer Association (DJR), B*Cured 2016 (DJR), funds from the Sylvester Cancer Center.

REFERENCES

1. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2006-2010. Neuro Oncol. 2013; 15: 1-56.
2. Cancer Facts & Figures 2014
3. Bloom HJ, Bessell EM. Medulloblastoma in adults: A review of 47 patients treated between 1952 and 1981. Int J Radiat Oncol Biol Phys. 1990; 18: 763-772.
4. Packer RJ, Cogen P, Vezina G, Rorke LB. Medulloblastoma: clinical and biologic aspects. Neuro Oncol. 1999; 1: 232-250.
5. Nejat F, Khashab ME, Rutka JT. Initial Management of Childhood Brain Tumors: Neurosurgical Considerations. J Child Neurol. 2008; 23: 1136-1148.
6. Schroeder K, Gururangan S. Molecular variants and mutations in medulloblastoma. Pharmacogenomics Pers Med. 2014; 7: 43-51.
7. Evans DG, Farndon PA, Burnell LD, Gattamaneni HR, Birch JM. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer. 1991; 64: 959-961.
8. Garrè ML, Cama A, Bagnasco F, Morana G, Giangaspero F, Brisigotti M, et al. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome--a new clinical perspective. Clin Cancer Res. 2009; 15: 2463-2471.
9. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, et al. The molecular basis of Turcot's syndrome. N Engl J Med. 1995; 332: 839-847.
10. Sorrell AD, Espenschied CR, Culver JO, Weitzel JN. TP53 Testing and Li-Fraumeni Syndrome: Current Status of Clinical Applications and Future Directions. Mol Diagn Ther. 2013; 17: 31-47.
11. Brandes AA, Palmisano V, Monfardini S. Medulloblastoma in adults: clinical characteristics and treatment. Cancer Treat. Rev. 1999; 25: 3-12.
12. Park TS, Hoffman HJ, Hendrick EB, Humphreys RP, Becker LE. Medulloblastoma: clinical presentation and management. Experience at the hospital for sick children, toronto, 1950-1980. J Neurosurg. 1983; 58: 543-552.
13. Massimino M, Biassoni V, Gandola L, Garrè ML, Gatta G, Giangaspero F, et al. Childhood medulloblastoma. Crit Rev Oncol Hematol. 2016; 105: 35-51.
14. Yazigi-Rivard L, Masserot C, Lachenaud J, Diebold-Pressac I, Aprahamian a, Avran D, et al. Childhood medulloblastoma. Arch Pediatr. 2008; 15: 1794-1804.
15. Radcliffe J, Bunin GR, Sutton LN, Goldwein JW, Phillips PC. Cognitive deficits in long-term survivors of childhood medulloblastoma and other noncortical tumors: Age-dependent effects of whole brain radiation. Int J Dev Neurosci. 1994; 12: 327-334.
16. Gottardo NG, Gajjar A. Chemotherapy for malignant brain tumors of childhood. J Child Neurol. 2008; 23: 1149-1159.
17. Parcker R, Vezina G. Management of and prognosis with medulloblastoma. Arch Neurol. 2008; 65: 1419-1424.
18. Merchant TE. Clinical controversies: Pediatric tumors. Semin Radiat Oncol. 2013; 23: 97-108.
19. Rekate HL, Grubb RL, Aram DM, Hahn JF, Ratcheson RA. Muteness of cerebellar origin. Arch Neurol. 1985; 42: 697-698.
20. Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer. 2003; 97: 663-673.
21. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol. 2001; 19: 3470-3476.
22. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol. 1998; 16: 1723-1728.
23. Packer RJ, Gurney JG, Punyko JA, Donaldson SS, Inskip PD, Stovall M, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. J Clin Oncol. 2003; 21: 3255-3261.
24. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.

J Natl. Cancer Inst. 2006; 98: 1528-1537.

25. Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. Cancer Causes Control. 1997; 8: 865-871.

26. Duffner PK, Krischer JP, Horowitz ME, Cohen ME, Burger PC, Friedman HS, et al. Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: a Pediatric Oncology Group study. Ann Neurol. 1998; 44: 313-316.

27. Yuh GE, Loredo LN, Yonemoto LT, Bush DA, Shahnazi K, Preston W, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. Cancer J. 2004; 10: 386-390.

28. Packer RJ, Vezina G. Management of and prognosis with medulloblastoma: therapy at a crossroads. Arch Neurol. 2008; 65: 1419-1424.

29. Northcott PA, Shih DJ, Remke M, Cho YJ, Kool M, Hawkins C, et al. Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. Acta Neuropathol. 2012; 123: 615-626.

30. Jenkin D, Shabanah MA, Shail EA, Gray A, Hassounah M, Khafaga Y, et al. Prognostic factors for medulloblastoma. Int J Radiat Oncol Biol Phys. 2000; 47: 573-584.

31. Ramaswamy V, Taylor MD. Medulloblastoma: From Myth to Molecular. J Clin Oncol. 2017; 35: 2355-2363.

32. Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, et al. Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature. 2002; 415: 436-442.

33. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling, et al. International Society Of Neuropathology--Haarlem International Society Of Neuropathology--Haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol. 2014; 24: 429-435.

34. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016; 131: 803-820.

35. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol. 2012; 123: 473-484.

36. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012; 123: 465-472.

37. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, et al. Intertumoral Heterogeneity within Medulloblastoma Subgroups. Cancer Cell. 2017; 31: 737-754.

38. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. Genes Dev. 2001; 15: 3059-3087.

39. Robbins DJ, Fei DL, Riobo NA. The Hedgehog signal transduction network. Sci Signal. 2012; 5: 6.

40. Oro AE. The Primary Cilia, a "Rab"-id Transit System for Hedgehog Signaling. Curr Opin Cell Biol. 2007; 19: 691-696.

41. Rohatgi R, Milenkovic L, Scott MP. Patched1 regulates hedgehog signaling at the primary cilium. Science. 2007; 317: 372-376.

42. Humke EW, Dorn KV, Milenkovic L, Scott MP, Rohatgi R. The output of Hedgehog signaling is controlled by the dynamic association between Suppressor of Fused and the Gli proteins. Genes Dev. 2010; 24: 670-682.

43. Aza-Blanc P, Lin HY, Ruiz i Altaba, A, Kornberg TB. Expression of the vertebrate Gli proteins in Drosophila reveals a distribution of activator and repressor activities. Development. 2000; 127: 4293-4301.

44. Méthot N, Basler K. Hedgehog controls limb development by regulating the activities of distinct transcriptional activator and repressor forms of Cubitus interruptus. Cell. 1999; 96: 819-831.

45. Wang B, Fallon JF, Beachy PA. Hedgehog-regulated processing of Gli3 produces an anterior/posterior repressor gradient in the developing vertebrate limb. Cell. 2000; 100: 423-434.

46. Dahmane N, Ruiz i Altaba A. Sonic hedgehog regulates the growth and patterning of the cerebellum. Development. 1999; 126: 3089-3100.

47. Wechsler-Reya RJ, Scott MP. Control of neuronal precursor proliferation in the cerebellum by Sonic Hedgehog. Neuron. 1999; 22: 103-114.

48. Kool M, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, et al. ICGC PedBrain Tumor Project of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell. 2014; 25: 393-405.

49. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, et al. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol. 2013; 31: 2927-2935.

50. Northcott PA, Buchhalter I, Morrissy AS, Hovestadt V, Weischenfeldt J, Ehrenberger T, et al. The whole-genome landscape of medulloblastoma subtypes. Nature. 2017; 547: 311-317.

51. Lee ST, Welch KD, Panter KE, Gardner DR, Garrossian M, Chang CW. Cyclopamine: From Cyclops Lambs to Cancer Treatment. J Agric Food Chem. 2014; 62: 7355-7362.

52. Kieran MW. Targeted treatment for sonic hedgehog-dependent medulloblastoma. Neuro Oncol. 2014; 16: 1037-1047.

53. Fellner C. Vismodegib (Erivedge) For Advanced Basal Cell Carcinoma. Pharm Ther. 2012; 37: 670-682.

54. Rudin CM, Hann CL, Laterra J, Yauch RL, Callahan CA, Fu L, et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med. 2009; 361: 1173-1178.

55. Yauch RL, Dijkgraaf GJ, Alicke B, Januario T, Ahn CP, Holcomb T, et al. Smoothened mutation confers resistance to a Hedgehog pathway inhibitor in medulloblastoma. Science. 2009; 326: 572-574.

56. Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, et al. Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. J Clin Oncol. 2015; 33: 2646-2654.

57. Metcalfe C, de Sauvage FJ. Hedgehog fights back: mechanisms of acquired resistance against Smoothened antagonists. Cancer Res. 2011; 71: 5057-5061.

58. Sharpe HJ, Pau G, Dijkgraaf GJ, Basset-Seguin N, Modrusan Z, Januario T, et al. Genomic analysis of smoothened inhibitor resistance in Basal cell carcinoma. Cancer Cell. 2015; 27: 327-341.

59. Kim J, Tang JY, Gong R, Kim J, Lee JJ, Clemons KV, et al. Itraconazole, a Commonly Used Antifungal that Inhibits Hedgehog Pathway Activity and Cancer Growth. Cancer Cell. 2010; 17: 388-399.

60. Lee MJ, Hatton BA, Villavicencio EH, Khanna PC, Friedman SD, Ditzler S, et al. Hedgehog pathway inhibitor saridegib (IPI-926) increases lifespan in a mouse medulloblastoma model. Proc Natl Acad Sci U S A.

2012; 109: 7859-7864.

61. Kim J, Aftab BT, Tang JY, Kim D, Lee AH, Rezaee M, et al. Itraconazole and Arsenic Trioxide Inhibit Hedgehog Pathway Activation and Tumor Growth Associated with Acquired Resistance to Smoothened Antagonists. Cancer Cell. 2013; 23: 23-34.

62. Rimkus T, Carpenter R, Qasem S, Chan M, Lo HW. Targeting the Sonic Hedgehog Signaling Pathway: Review of Smoothened and GLI Inhibitors. Cancers (Basel). 2016; 8: 22.

63. Kim J, Lee JJ, Kim J, Gardner D, Beachy PA. Arsenic antagonizes the Hedgehog pathway by preventing ciliary accumulation and reducing stability of the Gli2 transcriptional effector. Proc Natl Acad Sci U S A. 2010; 107: 13432-13437.

64. Beauchamp EM, Ringer L, Bulut G, Sajwan KP, Hall MD, Lee YC, et al. Arsenic trioxide inhibits human cancer cell growth and tumor development in mice by blocking Hedgehog/GLI pathway. J Clin Invest. 2011; 121: 148-160.

65. Antman KH. Introduction: the history of arsenic trioxide in cancer therapy. Oncologist. 2001; 2: 1-2.

66. Stanton BZ, Peng LF. Small-molecule modulators of the Sonic Hedgehog signaling pathway. Mol Biosyst. 2010; 6: 44-54.

67. Lin Z, Li S, Sheng H, Cai M, Ma LY, Hu L, et al. Suppression of GLI sensitizes medulloblastoma cells to mitochondria-mediated apoptosis. J Cancer Res Clin Oncol. 2016; 142: 2469-2478.

68. Gonnissen A, Isebaert S, Haustermans K. Hedgehog Signaling in Prostate Cancer and Its Therapeutic Implication. Int J Mol Sci. 2013; 14: 13979-14007.

69. Wickström M, Dyberg C, Shimokawa T, Milosevic J, Baryawno N, Fuskevåg OM, et al. Targeting the hedgehog signal transduction pathway at the level of GLI inhibits neuroblastoma cell growth *in vitro* and *in vivo*. Int J Cancer. 2013; 132: 1516-1524.

70. Li B, Fei DL, Flaveny CA, Dahmane N, Baubet V, Wang Z, et al. Pyrvinium attenuates Hedgehog signaling downstream of smoothened. Cancer Res. 2014; 74: 4811-4821.

71. Tang Y, Gholamin S, Schubert S, Willardson MI, Lee A, Bandopadhayay P, et al. Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition. Nat Med. 2014; 20: 732-740.

72. Long J, Li B, Rodriguez-Blanco J, Pastori C, Volmar CH, Wahlestedt C, et al. The BET bromodomain inhibitor I-BET151 acts downstream of smoothened protein to abrogate the growth of hedgehog protein-driven cancers. J Biol Chem. 2014; 289: 35494-35502.

73. Zhao Y, Yang CY, Wang S. The Making of I-BET762, a BET Bromodomain Inhibitor Now in Clinical Development. J Med Chem. 2013; 56: 7498-7500.

74. Buonamici S, Williams J, Morrissey M, Wang A, Guo R, Vattay A, et al. Interfering with resistance to smoothened antagonists by inhibition of the PI3K pathway in medulloblastoma. Sci Transl Med. 2010; 2: 51-70.

75. Zhao X, Ponomaryov T, Ornell KJ, Zhou P, Dabral SK, Pak E, et al. RAS/MAPK Activation Drives Resistance to Smo Inhibition, Metastasis, and Tumor Evolution in Shh Pathway-Dependent Tumors. Cancer Res. 2015; 75: 3623-3635.

76. Cohen JR, Resnick DZ, Niewiadomski P, Dong H, Liau LM, Waschek JA. Pituitary adenylyl cyclase activating polypeptide inhibits gli1 gene expression and proliferation in primary medulloblastoma derived tumorsphere cultures. BMC Cancer. 2010; 10: 676.

77. Morrissy AS, Cavalli FMG, Remke M, Ramaswamy V, Shih DJH, Holgado BL, et al. Spatial heterogeneity in medulloblastoma. Nat Genet. 2017; 49: 780-788.

78. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing. N Engl J Med. 2012; 366: 883-892.

Cite this article

Drozdowicz K, Long J, Winterbottom E, Robbins DJ, Rodriguez-Blanco J (2017) Targeting SHH-Subgroup Medulloblastoma. JSM Brain Sci 2(2): 1014.