Targeted treatment for sonic hedgehog-dependent medulloblastoma

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Novel treatment options, including targeted therapies, are needed for patients with medulloblastoma (MB), especially for those with high-risk or recurrent/relapsed disease. Four major molecular subgroups of MB have been identified, one of which is characterized by activation of the sonic hedgehog (SHH) pathway. Preclinical data suggest that inhibitors of the hedgehog (Hh) pathway could become valuable treatment options for patients with this subgroup of MB. Indeed, agents targeting the positive regulator of the pathway, smoothened (SMO), have demonstrated efficacy in a subset of patients with SHH MB. However, because of resistance and the presence of mutations downstream of SMO, not all patients with SHH MB respond to SMO inhibitors. The development of agents that target these resistance mechanisms and the potential for their combination with traditional chemotherapy and SHH inhibitors will be discussed. Due to its extensive molecular heterogeneity, the future of MB treatment is in personalized therapy, which may lead to improved efficacy and reduced toxicity. This will include the development of clinically available tests that can efficiently discern the SHH subgroup. The preliminary use of these tests in clinical trials is also discussed herein.

Keywords: expression profiling, hedgehog, medulloblastoma, targeted therapy.

Molecular studies have identified pathways involved in the tumorigenesis of many cancers including medulloblastoma (MB), the most common malignant brain tumor in young children.1,2 The hedgehog (Hh) pathway was first implicated in MB when germline mutations in patched (PTCH) were detected in patients with Gorlin syndrome, a heritable condition associated with an increased risk of MB and certain other cancers including basal cell carcinoma (BCC).3,4 Since that discovery, profiling studies and other genetic analyses have confirmed the involvement of the Hh pathway in the pathogenesis of MB and BCC.5–10 In addition, inhibitors of the Hh pathway have demonstrated efficacy in MB and BCC.11–19 Vismodegib recently became the first US Food and Drug Administration (FDA)-approved Hh pathway inhibitor based on antitumor activity observed in a phase 2 study in participants with advanced BCC.13,20 Vismodegib and other agents targeting the Hh pathway are currently being tested in clinical trials in participants with Hh-activated MB.21 The outcome of these trials may change the landscape of MB treatment, resulting in a more personalized approach with therapies that offer improved efficacy and reduced toxicity.

Unmet Need in Medulloblastoma

There is a significant need for targeted therapies in the treatment of patients with MB, especially those with high-risk or recurrent/relapsed disease.1,22 Patients with high-risk disease, including those younger than aged 3–6 years or those with metastatic disease, large cell or anaplastic histology, or poorly resected tumors,1,22–24 have lower survival rates than patients with standard-risk disease; 5-year survival rates are 55%–76% and 70%–85%, respectively.1,25 There is no effective salvage treatment for patients with recurrent/relapsed disease, and the prognosis for these patients is poor.22,26

In addition, most survivors suffer from long-term toxicities associated with the current standard-of-care treatment, which includes surgery followed by craniospinal radiation and chemotherapy.2,22,25–27 In particular, craniospinal radiation-induced neurocognitive toxicities, which are inversely related to patient age, can be severe.22,24,25,27 For this reason, craniospinal radiation is not recommended for patients younger than aged 3–6 years.22,24,25 In these patients, postsurgical chemotherapy is suggested and usually includes high-dose chemotherapy with stem-cell rescue.22

Classification of Medulloblastoma: A Focus on the Sonic Hedgehog Molecular Subgroup

The 4 major histological variants of MB according to the World Health Organization include classical, desmoplastic/nodular, MB with extensive nodularity, and anaplastic/large cell,28 each of
which is associated with distinct morphology. Patient age and prognosis have also been associated with the different variants.\textsuperscript{23,28} Recently, efforts to differentiate MB have shifted from histological to molecular classification. A consensus, based on gene expression profiling data from several independent laboratories,\textsuperscript{29–32} reports 4 molecular subgroups of MB:\textsuperscript{33} wingless (WNT; group 1), sonic hedgehog (SHH; group 2), group 3 (v-myc avian myelocytomatosis viral oncogene homolog [MYC] amplified), and group 4. Patient demographics, histology, DNA copy-number aberrations, and prognosis generally differ between the 4 molecular subgroups; however, there is some overlap among the 4 groups. Additional characteristics of the WNT group, group 3, and group 4 are reported in the consensus paper.\textsuperscript{33}

The SHH group is characterized by activated Hh pathway signaling.\textsuperscript{33} The Hh pathway is important for cell proliferation, differentiation, and survival during embryonic and fetal development\textsuperscript{9,34} and later, during postnatal development and adulthood, plays a role in bone development, stem cell maintenance, and maintenance and repair of some tissues.\textsuperscript{9,35,36} Hh signaling is initiated when 1 of 3 Hh ligands (SHH, Indian hedgehog, or desert hedgehog) binds to the transmembrane receptor PTC\textsubscript{H}, releasing its inhibition of the signal transducer smoothened (SMO).\textsuperscript{37} Activation of SMO initiates downstream signaling events, including release of glioma-associated oncogene (GLI) transcription factors from suppressor of fused (SUFU), a negative regulator of the pathway, allowing GLIs to translocate to the nucleus and induce expression of Hh pathway target genes (Fig. 1).\textsuperscript{37}

Aberrent expression of Hh-target genes leads to excessive cell proliferation and tumorigenesis.\textsuperscript{9,35} SHH signaling, which normally stimulates the proliferation of lineage-restricted cerebellar granule neuron precursors (CGNPs) during cerebellar development,\textsuperscript{38–40} can lead to MB formation when aberrantly activated.\textsuperscript{40–42} Mutations in PTC\textsubscript{H} and SUFU have been identified in up to 17% and 10% of MBs, respectively.\textsuperscript{43–46} Amplification of GLI2 has also been identified in MB.\textsuperscript{47–50}

In addition to aberrant SHH signaling, the SHH subgroup is sometimes characterized by v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN) expression, gain of chromosome 3q, p53 mutations, and amplification of MYCN.\textsuperscript{47,51} The SHH subgroup is most prevalent in infants (<aged 4 years) and adolescents/adults (>aged 16 years) and less common in children aged 4–16 years (Fig. 2).\textsuperscript{5,52} This subgroup comprises all histological subtypes and does not often metastasize,\textsuperscript{53,54} with recurrences mainly occurring locally.\textsuperscript{52} Prognosis for patients with SHH-activated MB is intermediate.\textsuperscript{5,50,53,54}

Pediatric and adult patients with SHH-activated MB are distinct from one another in terms of genomic alterations, metastasis, and prognosis.\textsuperscript{55} A recent genomic sequencing analysis of adult and pediatric patients with SHH-activated MB identified age-dependent subgroups including those with \textit{PTCH1} mutations (across all age groups), SUFU mutations (infants), and SMO mutations (adults).\textsuperscript{49} Downstream amplifications of MYCN and GLI2 as well as mutations in \textit{p53} were identified in children between the ages of 4–17 years but were rarely observed in infants and adults.\textsuperscript{49} MBs with mutations in \textit{p53} have been associated with Li-Fraumeni syndrome and a worse overall prognosis.\textsuperscript{51} Overexpression of the chemokine receptor CXCR4 has been observed in young patients with desmoplastic histology.\textsuperscript{55} Data from a meta-analysis of 550 tumor samples from patients with MB (28% SHH) showed that metastasis was more common in infants (<aged 4 years, 17%) and children (aged 4–16 years, 22%) with SHH-activated MB than in adults.\textsuperscript{8} In another study of 66 SHH MBs, metastasis was found to be a marker for poor prognosis in adults but not in children.\textsuperscript{47} Survival data from the meta-analysis showed that 10-year overall survival (OS) in patients with SHH tumors is much higher in infants (77%) than in children (51%) and adults (34%).\textsuperscript{8} This may be due in part to the high percentage of infants with desmoplastic histology, which has been associated with a more favorable prognosis. In the analysis of 66 SHH MBs, children with desmoplastic histology were shown to have a better prognosis than children with classic histology; in contrast, desmoplastic histology was not prognostic for adults.\textsuperscript{55} Interestingly, adults with SHH MB carrying chromosomal alterations (2 gain, 10q deletion, 17q gain, 17p deletion) and/or GLI2 amplification have a much worse prognosis than children carrying the same genetic aberrations;\textsuperscript{47} however, the reasons for this difference are unclear and may relate to regimen intensity rather than chromosomal alterations.

### Preclinical Evidence Supporting the Role of Hh Signaling in Medulloblastoma

Numerous preclinical studies have identified a role for the Hh pathway in the tumorigenesis of MB and further demonstrated that inhibition of the Hh pathway impedes tumor growth. Mouse models of MB, such as \textit{Pch\textsubscript{null}}, \textit{Pch\textsuperscript{v–v}}, \textit{p53–p53}, and \textit{Pch\textsuperscript{v–v}} hypermethylated in cancer 1 [Hic1]\textsuperscript{v–v}, have been particularly useful for in vivo preclinical testing of Hh inhibitors because tumor cells cultured in vitro may differ from in vivo tumors with respect to biological characteristics and responses.\textsuperscript{54,55} In mouse models, treatment with inhibitors of SMO, the positive regulator of the Hh signaling pathway, leads to reduced tumor growth\textsuperscript{54,56–59} and increased survival.\textsuperscript{55}

Hh pathway targets that may contribute to Hh-dependent MB tumorigenesis have been identified (Table 1). In MB cells and tumor models, SHH signaling has been shown to induce expression and/or stabilization of MYCN, miR-17-19, Snai1, CXC4, Math1/Atoh1, cyclin D1, Sox2, Sox9, abnormal spindle-like microcephaly-associated, Bmi1, and Bcl2 in CGNPs and brain tumor initiating cells (BTICs), leading to increased proliferation and tumor growth.\textsuperscript{53,60–71} Inhibition or deletion of these targets reduces cell proliferation and tumor growth in MB models.\textsuperscript{53,64,66,72} In addition, several studies have shown that SHH-mediated metabolic programming increases MB tumor progression.\textsuperscript{73–75}

Signaling pathways that interact with Hh signaling in MB have also been identified (Table 2). Expression of components of the insulin growth factor (IGF), placental growth factor, phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), WNT, and Notch pathways have been identified in SHH-treated CGNPs and SHH-mediated MBs.\textsuperscript{74–81} Activation of these pathways is required for and/or enhances SHH-induced MB formation.\textsuperscript{76,80–81} SHH signaling (proliferation) and IGF signaling (survival) also converge to regulate MYCN- and yes-associated protein (YAP)-mediated cell cycle control in CGNPs.\textsuperscript{54–68} Conversely, pituitary adenylate cyclase-activating polypeptide (PACAP)/cyclic adenosine monophosphate-dependent protein kinase A (PKA) signaling may antagonize Hh signaling in Hh-dependent MB.\textsuperscript{37,88}
Methods Being Employed to Identify SHH-activated Medulloblastoma and Their Use in the Clinic

Immunohistochemistry (IHC) and/or reverse-transcriptase polymerase chain reaction (RT-PCR) have been used to assess Hh pathway activity in patients with cancer based on GLI1 expression in hair, skin, and tumor biopsies. These methods have been used in several phase 1 trials of SMO inhibitors to determine Hh pathway activity and confirm targeted inhibition of the pathway. However, no IHC-based grouping of these tumors has been validated, and interobserver variability in identifying positive staining limits its clinical utility for patient stratification. Furthermore, due to cost and time constraints, these methods are not amenable for use as a patient preselection tool in large randomized trials.

Gene expression profiling methods in combination with IHC and/or RT-PCR have been used to identify MB subgroups in archival tumor samples. Several groups have used published profiling data to identify gene signatures specific to the different MB subgroups including the SHH subgroup. In addition, the assays developed have been optimized for use in the clinic; they are quicker, more cost-effective, and require less RNA than standard profiling techniques. Schwalbe et al identified an 8-gene SHH signature (BCHE, GLI1, ITIH2, MICAL1, PDLIM3, PTCH2, RAB33A, and SFRP1) for use in snap-frozen tumor samples. Northcott et al identified a 5-gene SHH signature (PDLIM3, EYA1, HHIP, ATOH1, and SFRP1) optimized for use in formalin-fixed paraffin-embedded (FFPE)
tumor samples. At the American Association for Cancer Research annual meeting in 2012, Amakye et al presented the development of their unique 5-gene SHH signature (GLI1, SPHK1, SHROOM2, PDLIM3, and OTX2), which has also been optimized for use in FFPE tumor samples.

The 5-gene SHH signature identified by Amakye et al received an investigational device exemption from the FDA for use in a clinical trial (NCT01708174; a phase 3 study of oral sonidegib (LDE225) vs temozolomide [TMZ] in participants with HH pathway-activated relapsed MB; Novartis documentation on file), and to date it is the only signature that has shown an association with tumor response in participants treated with an HH pathway inhibitor.

Data presented at the Society for Neuro-Oncologic Scientific Meeting in 2013 showed that, in 41 MB tumors from participants treated with sonidegib in 3 independent trials (adults with advanced solid tumors [NCT00880308], East Asian adults with advanced solid tumors [NCT01208831], and children with tumors potentially dependent on the HH pathway [phase 1; NCT01125800]; Table 3), all who responded to sonidegib treatment were predicted to have HH pathway-activated tumors using the 5-gene HH signature.

### Table 1. Preclinical evidence supporting the role of hedgehog pathway targets in medulloblastoma tumorigenesis

<table>
<thead>
<tr>
<th>Hh Pathway Target</th>
<th>Effects of Activated Hh Signaling</th>
<th>Suspected Role in MB Tumorigenesis</th>
<th>Effects of Targeted Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYCN</td>
<td>Increased expression in CGNPs</td>
<td>Induces miR-17/92 expression in CGNPs, promoting their proliferation</td>
<td>Anti-miR-17 and -19 reduced growth of MB tumor allografts (flank and brain) and prolonged survival in mice with intracranial transplants</td>
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<tr>
<td>Snail1</td>
<td>Increased expression in GCPs, mouse MB models, and human MB-derived cell lines</td>
<td>Induces cell proliferation and transformation through induction of MYCN transcription</td>
<td></td>
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<tr>
<td>CXCR4</td>
<td>Induces cell surface localization and effector signaling in MB cells</td>
<td>Causes pro-growth transcriptional response (increased expression of Math1/Atoh1 and cyclin D1) and increased tumor growth</td>
<td>CXCR4-specific antagonists, AMD3100 and AMD3465, inhibited growth of MB tumor xenografts</td>
</tr>
<tr>
<td>Sox2</td>
<td>Increased expression in CGNPs and Sox2-positive MB in mouse models</td>
<td>Overexpression leads to proliferation</td>
<td>Deletion of Sox2 in primary CGNP cultures with constitutive SHH signaling led to decreased proliferation</td>
</tr>
<tr>
<td>Sox9</td>
<td>Increased expression in SHH MB</td>
<td>Activation during embryogenesis leads to SHH-dependent MB; suppression during postnatal development promotes SHH-independent MB</td>
<td></td>
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<tr>
<td>ASPM</td>
<td>Increased expression in CGNPs</td>
<td>Sustains the progenitor phenotype of CGNPs</td>
<td>ASPM knock-out led to decreased proliferative capacity and self-renewal</td>
</tr>
<tr>
<td>Bmi1</td>
<td>Drives expression in BTICs</td>
<td>Contributes to SHH-mediated expansion of GCPs through direct regulation of the cyclin-dependent kinase inhibitor p21 Waf1/Cip1 and modulation of other cell cycle inhibitors and TGFβ pathway targets; positive feedback loop between Bmi1 and SHH in BTICs; may regulate the SHH pathway through transcriptional silencing of the E3 ubiquitin ligase Culin3</td>
<td></td>
</tr>
<tr>
<td>Bcl2</td>
<td>Increased expression</td>
<td>Increases proliferation and decreases apoptosis of SHH-induced MB</td>
<td>Fatty acid synthase-specific inhibitor C75 inhibited MB cell proliferation, promoted MB cell death, and prolonged survival in MB-bearing mice</td>
</tr>
<tr>
<td>Lipids</td>
<td>Lipid accumulation, increased lipogenic enzyme expression, and suppression of fatty acid oxidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPARγ</td>
<td>Increased expression in MB cells</td>
<td>Induces glycolysis</td>
<td>PPARγ-specific inhibitor, GW9662, blocked CGNP proliferation, drove MB cell death, and prolonged survival of mice with MBs (NeuroD2-SmoA1)</td>
</tr>
</tbody>
</table>

Abbreviations: ASPM, abnormal spindle-like microencephaly-associated; Atoh1, atonal homolog 1; BTIC, brain tumor initiating cell; CGNP, cerebellar granule neuron progenitor; GCP, granule cell progenitor; MB, medulloblastoma; MYCN, v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; PPARγ, peroxisome proliferator-activated receptor gamma; SHH, sonic hedgehog; Sox, sex determining region Y; TGFβ, transforming growth factor beta.
Three of 4 adults with Hh-activated MB responded (3 partial responses [PRs]). Two patients (1 child, 1 adult) with Hh-activated MB had progressive disease. The reason for lack of response in these individuals is unknown but may be due to mutations downstream of SMO. The remaining 34 participants, who were predicted to have Hh pathway-nonactivated tumors, did not respond (5 stable disease, 28 progressive disease) or were not assessed (n = 1). In the phase 1 study in children with recurrent/refractory MB or other tumors potentially dependent on the Hh pathway (NCT01125800), only participants with MB responded. A phase 2 portion of the trial in pediatric and adult patients with recurrent or refractory MB has recently completed accrual (NCT01125800). The phase 3 trial in participants with relapsed Hh-activated MB described earlier is currently recruiting (NCT01708174). Participants will be treated with sonidegib or TMZ. Participants with TMZ-naive Hh-activated MB, as determined by the 5-gene signature assay mentioned above, who have relapsed following standard therapy will be eligible for randomization (2:1, sonidegib:TMZ). Participants who have previously...
been treated with TMZ or children aged 6 years who are not candidates for or have declined radiotherapy will be eligible for a non-randomized portion of the trial. The primary endpoint is overall response rate. Secondary endpoints include progression-free survival (PFS), duration of response (DoR), OS, safety, pharmacokinetics, and effects of sonidegib on Hh pathway biomarkers.

The only other Hh pathway inhibitor being tested specifically in participants with MB is the SMO inhibitor vismodegib (GDC-0449; Table 3). A PR was demonstrated in a participant with metastatic MB, supratentorial primitive neuroectodermal tumors, or atypical teratoid rhabdoid tumors (NCT00085202). A summary of clinical studies evaluating Hh pathway inhibitors in participants with MB is provided in Table 3.

### SHH-activated Tumors Downstream of SMO: Combating Resistance to SMO Inhibitors

Resistance to SMO inhibitors has been observed in preclinical MB mouse models, and in at least 1 patient with MB in the clinic. The observed resistance has been attributed to acquired mutations in SMO ([D473H in human SMO], G457S, and E518), amplification of GLI2, MYCN, and cyclin D1, upregulation of the IGF-1R-PI3K pathway (SUFU and PTEN are closely linked on chromosome 10), and upregulation of the adenosine triphosphate-binding cassette transporter p-glycoprotein substrate, which is a common mechanism of drug resistance in cancer cells. In addition, a truncated version of GLI1, identified in MB cells, was shown to render MB cells resistant to the SMO inhibitors cyclopamine and vismodegib. As discussed earlier, results from preclinical studies suggest that the WNT pathway may interact with Hh signaling in MB, and cross talk between these pathways has also been observed.
been described in gastrointestinal cancers in which Hh pathway activation was shown to suppress WNT signaling, leading to decreased proliferation of cancer cells. However, WNT pathway activation in MB as a result of treatment with SHH inhibitors has not been reported.

Potential mechanisms for overcoming resistance to SMO inhibitors in MB and other tumor types have been identified, including inhibitors that bind and inhibit mutant SMO. These novel SMO antagonists have binding sites that are distinct from those currently being investigated in the clinic and are capable of inhibiting both wild-type and mutant SMO. 

Active8, one small molecule inhibitor with activity against the SMO variant D477G (identified in the participant who relapsed after treatment with vismodegib) was shown to inhibit Hh activity in MB mouse models and may provide additional activity in combination with different classes of SMO inhibitors to help prevent resistance.

Inhibitors that target downstream components of the Hh pathway may also be useful for overcoming resistance to SMO inhibitors. Several inhibitors that target GLI have been identified in cellular screens. The small molecule inhibitors, GANT58 and GANT61, which primarily target nuclear GLI, were shown to inhibit in vitro tumor cell proliferation and block cell growth in a prostate xenograft model. In neuroblastoma cells, GANT61 treatment caused downregulation of GLI1, MYC, MYCN, and cyclin D1 and was shown to inhibit Hh signaling more effectively than SMO inhibitors. Moreover, in neuroblastoma xenografts, GANT61 enhanced the effects of chemotherapy, further reducing tumor growth. Four additional Hh pathway inhibitors (HPI 1–4), each with differential effects on GLI processing and stability, trafficking to the primary cilium, and ciliogenesis, were also identified. Two of the 4 HPIs were capable of blocking the proliferation of neural progenitors in CGNs from Math1-Cre:SMO-M2 mice and reduced expression of GlI1, GlI2, N-Myc, and cyclin D1 protein. Another novel compound, pyrrolo[3,2-c]quinoline-4-one derivative 12b, was shown to suppress stromal GlI1 mRNA expression and demonstrated antitumor activity in an MB mouse allograft. In addition to novel compounds, arsenic trioxide (ATO), an FDA-approved anticancer therapy, was also shown to inhibit GLI1 in GLI-dependent cancer cell lines and increase survival of MB mouse models. In a second study, treatment with ATO inhibited growth of Hh-driven MB models. This study suggested that ATO blocked Hh-induced ciliary accumulation of GLI2 and reduced GLI2 stability, whereas the previous study suggested that GLI1 was inhibited in the nucleus, independent of the primary cilium. Resistance to SMO inhibitors could also be overcome through activation or inhibition of other signaling pathways such as PKA and PI3K. Based on the observation that PACAP-dependent PKA signaling may antagonize Hh signaling in Hh-dependent primary MB tumorsphere cultures, its activation in tumor cells via activation of PACAP receptors may provide a SMO-independent mechanism to inhibit aberrant Hh signaling and thus inhibit MB growth. Conversely, inhibition of PI3K signaling in SMO inhibitor-resistant tumors or in combination with SMO inhibitors has been shown to inhibit MB growth. Treatment of vismodegib-resistant tumor models with the PI3K inhibitor GDC-0941 caused tumor growth inhibition. Similarly, inhibition of PI3K signaling using buparlisib (BKM120; another PI3K inhibitor) or BEZ235 (a dual PI3K/mTOR inhibitor) in combination with sonidegib delayed or inhibited the resistance observed in mouse MB models treated with sonidegib alone. Based on these preclinical data, a phase 1 study of sonidegib in combination with buparlisib in participants with advanced solid tumors is ongoing (NCT01576666). The p90 ribosomal S6 kinase inhibitor BI-D1870, which was identified in a screen against cells resistant to SHH inhibitors, was shown to induce apoptosis, restrict colony formation, and sensitize cells to chemotherapy. BI-D1870 showed activity in BTICs and in primary human samples. Age-based therapeutic combinations have also been suggested following the genomic sequencing analysis discussed above. Based on these results, combinations of SMO inhibitors with epigenetic modifiers or PI3K pathway inhibitors in adults and GLI inhibitors in children would be predicted to have improved activity.

Other agents that affect Hh signaling may provide benefit to patients with resistance to SMO inhibitors. The systemic antifungal itraconazole was identified in a screen as a potent inhibitor of Hh signaling. Itraconazole inhibited tumor growth in an MB allograft model by preventing the ciliary localization of SMO. Itraconazole was also shown to inhibit Hh signaling in SMO-mutant models. In MB cells and mice with intracranial drug-resistant SMO-D477G MB (or wild-type SMO), itraconazole alone or in combination with ATO inhibited tumor growth. Combination treatment led to greater inhibition and improved survival compared with treatment with either agent alone. These agents were efficacious in all reported drug-resistant SMO mutants and in wild-type SMO. A class of glucocorticoids (budesonide, ciclesonide) has also been shown to inhibit ciliary localization of SMO in Hh-responsive cells. Inhibition of SMO ciliary localization was coupled with inhibition of Hh signaling activity in cells with wild-type and mutant SMO (resistant to SMO inhibitors). Finally, botanicals are also being investigated as second-generation drugs that may benefit patients who have developed resistance to SMO inhibitors.

Conclusions

Numerous preclinical and molecular profiling studies have implicated the Hh signaling pathway in the pathogenesis of MB. Several Hh pathway inhibitors have been developed and are being tested in the clinic. Two of these inhibitors, both targeting SMO, have shown efficacy in patients with Hh-activated MB. Other inhibitors that target different components of Hh signaling, including those that target SMO mutants, GLIs, and ciliary localization of GLI or SMO, are now being developed. Regardless of the mode of Hh pathway inhibition, selection of patients with SHH-activated MB is critical for identifying those who would benefit from this therapy and preventing unnecessary potential toxicities associated with current standard-of-care therapies, especially in young children. Ongoing and future studies of Hh pathway inhibitors incorporating screening procedures that utilize IHC or gene signatures to identify SHH-activated MB will likely improve the way patients with MB are treated.

Acknowledgments

The author thanks Jillian Brechbiel, PhD, and Karen Kaluza, PhD, for medical editorial assistance with this manuscript. Financial support for editorial assistance was provided by Novartis Pharmaceuticals Corporation.
Kieran: Hedgehog pathway inhibitors in medulloblastoma

Funding
Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

Conflict of interest statement: Mark W. Kieran has acted as a consultant/advisor for Novartis Pharmaceuticals Corporation and has received speaker honoraria and research funding from Novartis Pharmaceuticals Corporation.

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