Medulloblastoma in the age of molecular subgroups: a review

JNSPG 75th Anniversary Invited Review Article

Kyle Juraschka, MD,^{1–4} and Michael D. Taylor, MD, PhD^{1–4}

¹Division of Neurosurgery; ²The Arthur and Sonia Labatt Brain Tumor Research Centre, The Hospital for Sick Children; and Departments of ³Laboratory Medicine and Pathobiology and ⁴Surgery, University of Toronto, Ontario, Canada

Medulloblastoma is the most common pediatric malignant brain tumor. Advances in molecular profiling have uncovered significant heterogeneity among medulloblastomas and led to the identification of four distinct subgroups (wingless [WNT], sonic hedgehog [SHH], group 3, and group 4) that represent distinct disease entities in both underlying biology and clinical characteristics. The rapidly expanding repertoire of tools to study developmental and cancer biology is providing a wealth of knowledge about these embryonal tumors and is continuously refining the understanding of this complex cancer. In this review, the history of discovery in medulloblastoma is discussed, setting a foundation to outline the current state of understanding of the molecular underpinnings of this disease, with a focus on genomic events that define the aforementioned subgroups and evolving areas of focus, such as the cell of origin of medulloblastoma and medulloblastoma subtypes. With these recent discoveries in mind, the current state of medulloblastoma treatment and clinical trials is reviewed, including a novel risk stratification system that accounts for the molecular biomarkers of patients with a high risk for refractory disease. Lastly, critical areas of focus for future basic science and clinical research on this disease are discussed, such as the complexities of medulloblastoma metastases and recurrence as well as the priorities and strategies to implement in future clinical trials.

<https://thejns.org/doi/abs/10.3171/2019.5.PEDS18381>

KEYWORDS medulloblastoma; oncology; neurooncology; genomics; metastasis

MEDULLOBLASTOMA is the most common malignant (WHO grade IV) brain tumor of childhood and is an embryonal lesion thought to arise from progenitor cell populations present during early brain development.^{17,31,67} Medulloblastoma is currently treated with maximal safe resection, chemotherapy, and craniospinal radiation. Despite such aggressive multimodal therapy, approximately 30% of patients eventually succumb to this disease, and survivors cope with the long-term side effects of treatment that have significant impacts on their quality of life.^{12,18,20,35,41,42,66}

Initial descriptions of medulloblastoma date back to Harvey Cushing, who initially described medulloblastoma as a subset of gliomas (Fig. 1).^{2,11,57} He detailed many key features of these tumors, including their tendency to arise from the cerebellar vermis and to exhibit leptomeningeal metastasis.¹¹ Along with neuropathologist Percival Bailey, Cushing described medulloblastoma histopathologically as containing numerous mitoses, small round nuclei, and minimal cytoplasm.² The two recognized that medullo-

blastoma cells resembled undifferentiated cells present in embryonal stages and posited that medulloblastoma arose from “medulloblasts,” multipotent stem cells thought to be present in the neural tube.^{2,26,32,57} While no such single primitive cell type exists, Cushing and Percival’s foundational work in defining the clinical characteristics, operative technique, and histopathology of this tumor formed our basic understanding of medulloblastoma, which is now being refined in the molecular era.⁵⁷

While some early medulloblastoma patients were treated with radiation sporadically, the first landmark change in the management of these tumors came in 1953, when a study of 27 patients with medulloblastoma demonstrated significantly improved survival after receiving craniospinal radiation.^{44,57} Routine craniospinal radiation improved survival to approximately 60%.⁴⁴ The next intriguing progression in our understanding of this disease occurred in 1973 in a study in which the authors proposed that medulloblastoma be classified as a primitive neuroectodermal tumor (PNET) because of histological similarities and a

ABBREVIATIONS GTR = gross-total resection; NTR = near-total resection; PFS = progression-free survival; SHH = sonic hedgehog; WNT = wingless.

SUBMITTED May 14, 2019. **ACCEPTED** May 28, 2019.

INCLUDE WHEN CITING DOI: 10.3171/2019.5.PEDS18381.

FIG. 1. Timeline of key discoveries in medulloblastoma, culminating in the definition of the four molecular subgroups. Photograph of Dr. Harvey Williams Cushing. Source: <https://wellcomecollection.org/works/nzkqj47t?wellcomelimagesUrl=/indexplus/image/V0027585.html>. Courtesy of The Wellcome Trust, CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/deed.en>). Sketch and photomicrograph reproduced from Cushing H: Experiences with the cerebellar medulloblastomas. *Acta Pathologica Microbiologica Scandinavica* 7:1–86, 1930. Public domain. Photograph of a young girl receiving chemotherapy. Source: <https://visualsonline.cancer.gov/details.cfm?imageid=2192>. Photographer: Bill Branson. Public domain. National Cancer Institute AV Number: AV-8503-3438. Figure is available in color online only.

hypothesis that medulloblastoma and other PNETs arise from undifferentiated cells in the subependymal zone.¹⁶ Finally, the addition of cytotoxic chemotherapy regimens as standard of care, starting with trials in the 1970s, improved the 5-year survival risk for average-risk disease to 70%–80% and for high-risk disease to 60%–65%.^{5,20,41}

Rapid advances in molecular genetics over the past two decades have provided significant advancements in our understanding of medulloblastoma. This tumor entered the molecular era, beginning with gene expression array studies demonstrating that medulloblastoma is a distinct entity from other embryonal central nervous system tumors.⁴⁷ Multiple independent groups performed transcriptional profiling on medulloblastoma samples and reached consensus on four distinct molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.^{8,25,37,52,63} Molecular subgrouping has already influenced the design of contemporary clinical trials and refined pre-clinical studies of medulloblastoma, and these subgroups were adopted into the 2016 WHO classification of tumors of the central nervous system.³¹ The expanding wealth of molecular data from patient samples has started to allow

further refinement of these subgroups, with numerous subtypes of medulloblastoma being recognized.^{7,36,59}

In this review, our current understanding of this fascinating disease will be reviewed, including the molecular underpinnings of this disease, risk stratification, treatment protocols, and the landscape of current clinical trials. Subsequently, key areas of future inquiry in basic science and clinical trials will be discussed.

Epidemiology

Medulloblastoma accounts for approximately 20% of all childhood brain tumors and 63% of intracranial embryonal tumors.⁴⁰ These tumors can arise throughout childhood and into adulthood with an overall annual incidence of approximately 5 cases per 1 million in the pediatric population.⁴⁰ Seventy percent of medulloblastomas occur in children under the age of 10, with incidence peaking in children 1–4 and 5–9 years of age.^{23,40} Overall, medulloblastoma is more common in males, affecting approximately 1.7 times more males than females,^{23,40} although sex predilection as well as age-specific incidence

Subgroup		WNT	SHH	Group 3	Group 4
Clinical Characteristics	% of Cases	10	30	25	35
	Age at Diagnosis
	Gender Ratio (M:F)	1:1	1:1	2:1	3:1
	Anatomic Location
	Histology	Classic, Rarely LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
	Metastasis at Diagnosis (%)	5-10	15-20	40-45	35-40
	Recurrence Pattern	Rare; Local or metastatic	Local	Metastatic	Metastatic
	Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Molecular Characteristics	Proposed Cell of Origin	Progenitor cells in the lower rhombic lip	Granule precursors of the external granule layer	Neural stem cells	Unipolar brush cells
	Recurrent Gene Amplifications	-	<i>MYCN</i> <i>GLI1</i> or <i>GLI2</i>	<i>MYC</i> <i>MYCN</i> <i>OTX2</i>	<i>SNCAIP</i> <i>MYCN</i> <i>OTX2</i> <i>CDK6</i>
	Recurrent SNVs	<i>CTNNB1</i> <i>DDX3X</i> <i>SMARCA4</i> <i>TP53</i>	<i>PTCH1</i> <i>TERT</i> <i>SUFU</i> <i>SMO</i> <i>TP53</i>	<i>SMARCA4</i> <i>KBTBD4</i> <i>CTDNEP1</i> <i>KMT2D</i>	<i>KDM6A</i> <i>ZMYM3</i> <i>KTM2C</i> <i>KBTBD4</i>
	Cytogenetic Events Gain Loss	6	3q, 9p 9q, 10q, 17p	1q, 7, 18 8, 10q, 11, 16q i17q	7, 18q 8, 11p, X i17q
	Other Recurrent Genetic Events	-	-	<i>GFI1</i> and <i>GFI1B</i> enhancer hijacking	<i>PRDM6</i> , <i>GFI1</i> , and <i>GFI1B</i> enhancer hijacking

Age: Infant Child Adult

FIG. 2. The molecular subgroups of medulloblastoma, based on data from the following references.^{36,37,61} LCA = large cell/anaplastic; SNV = single-nucleotide variant. Figure is available in color online only.

vary by subgroup (Fig. 2).⁶¹ Medulloblastoma is far more rare in adulthood, with a reported incidence of 0.05 cases per 100,000 population.⁴⁰

Primary risk factors for the development of medulloblastoma include hereditary cancer predisposition syndromes. Germline mutations in WNT signaling pathway genes, such as *APC* mutations, which occur in Turcot syndrome, can predispose to WNT medulloblastoma.⁷⁰ SHH medulloblastomas may be initiated by germline mutations in *PTCH1* (Gorlin syndrome), *SUFU*, *TP53* (Li-Fraumeni syndrome), or *SMO* (Curry-Jones syndrome).^{6,60,64,70} Numerous other cancer predisposition syndromes have been associated with medulloblastoma, although with a lower

risk of medulloblastoma development than the aforementioned syndromes associated with WNT and SHH tumors.⁷⁰

Molecular Subgroups of Medulloblastoma

WNT

WNT subgroup medulloblastomas account for approximately 10% of all medulloblastomas.⁶¹ These tumors typically occur in children over the age of 4 and adolescents and affect an equal number of males and females.⁶¹ They are typically located midline with involvement of the brainstem or in the cerebellar peduncle and cerebello-

pontine angle cistern.⁴⁶ The WNT subgroup is associated with an excellent prognosis (> 95% survival at 5 years in pediatric patients), is rarely metastatic at diagnosis (5%–10% of cases), and rarely recurs.^{9,61}

WNT medulloblastoma is thought to arise from progenitor cells in the lower rhombic lip of the developing brainstem.^{17,67} Approximately 90% of WNT tumors contain a mutation in *CTNNB1*, which encodes β -catenin.³⁶ This mutation causes the WNT signaling pathway to be constitutively active, driving expression of WNT responsive genes that promote tumor proliferation.⁶¹ Mutations in the *APC* tumor suppressor gene account for the majority of WNT tumors that lack *CTNNB1* mutations.^{61,70} Other recurrently mutated genes identified in this subgroup include *DDX3X* (36%), *SMARCA4* (19%), *TP53* (14%), *CSNK2B* (14%), *PIK3CA* (11%), and *EPHA7* (8%).^{22,36,48,54} Monosomy 6 is also characteristic of WNT tumors (80%–85% of cases) and typically coincides with *CTNNB1* mutations.³⁶ Aside from monosomy 6, WNT tumors have balanced genomes and rarely contain copy number aberrations.³⁷

Building on the classification of medulloblastoma into subgroups, recent integrated analysis of DNA methylation, gene expression, copy number alterations, and clinical data has suggested the existence of subtypes of medulloblastoma within each subgroup.⁷ Using gene expression and methylation array data, Cavalli et al. suggested the existence of two WNT subtypes: WNT α and WNT β .⁷ The WNT α subtype primarily occurred in children and 98% of these cases had monosomy 6, whereas the WNT β subtype occurred in older children and adults and infrequently (29%) had monosomy 6.⁷

SHH

The SHH subgroup has a balanced sex ratio and a bimodal peak age incidence, most often occurring in infants and adults, accounting for two-thirds of medulloblastoma cases in these age groups.^{24,61} Approximately 30% of medulloblastomas are classified as SHH tumors.⁶¹ They characteristically arise in the cerebellar hemispheres, rather than the midline location characteristic of other subgroups.⁴⁶ Outcomes in this subgroup vary according to clinical (age and metastatic status) and molecular (*MYCN* amplification and *TP53* mutation status) characteristics.^{7,50}

SHH tumors are thought to arise from granule cell precursors of the external granule layer.^{17,67} The majority of these tumors contain germline or somatic mutations or copy number alterations in the SHH signaling pathway, leading to constitutively activated SHH signaling, driving tumor development and progression. Commonly mutated or deleted SHH genes include *PTCH1* (43%) and *SUFU* (10%).³⁶ Activating mutations of *SMO* (9%) and amplifications in *GLI1* or *GLI2* (9%) and *MYCN* (7%) are also frequently observed.³⁶ In addition, recurrent alterations in the *TP53* signaling pathway (9.4%) and the PI3K pathway (10%) may also act as key drivers of tumorigenesis in this subgroup.³⁹ *TERT* promoter mutations are also found in 39% of SHH tumors (including nearly all adult SHH cases).^{7,36} Frequently occurring cytogenetic events in this group include loss of chromosome 9q (causing loss of heterozygosity of *PTCH1*) and 10q (loss of *SUFU*).³⁶

Up to four different SHH subtypes have been de-

scribed.^{7,56,59} One study of childhood (age 0–16 years) medulloblastoma defined two subtypes based on comprehensive molecular profiling: childhood (age 4.3 and older) and infant (under 4.3 years).⁵⁹ Four SHH subtypes were described by Cavalli et al.: SHH α , SHH β , SHH γ , and SHH δ . SHH α occurs in childhood and is characterized by frequent *TP53* mutations and *MYCN/GLI2* amplifications.⁷ SHH β occurs in infants, is frequently metastatic, and is associated with a poor outcome compared to that with SHH γ , which also occurs in infants and is associated with medulloblastoma with extensive nodularity (MBEN) histology.⁷ Finally, the SHH δ subtype occurs in adults and is enriched for *TERT* promoter mutations.⁷

Group 3

Group 3 medulloblastoma has a male predominance and occurs nearly exclusively in infants and young children.⁶¹ This subgroup accounts for approximately 25% of all medulloblastoma cases and is associated with high rates of metastasis at diagnosis (40%–45%) and the worst survival outcomes of any subgroup (under 60% at 5 years).⁶¹ Radiographically, these tumors typically demonstrate a midline vermian location adjacent to the fourth ventricle.⁴⁶

Group 3 tumors likely arise from a neural stem cell population.^{17,67} Unlike the SHH and WNT subgroup tumors, integrated molecular analyses have not identified a common driver pathway that defines the group 3 and group 4 subgroups. Nonetheless, a commonly recurring aberration is *MYC* amplification (17%), an event that frequently co-occurs with *PVT1-MYC* fusions.^{36,39} Recurrent somatic mutations are rare in group 3 tumors, with only four genes mutated in over 5% of cases (*SMARCA4*, *KBTBD4*, *CTDNEP1*, and *KMT2D*).³⁶ Small subsets of these tumors are driven by amplifications of *MYCN* (5%) and the transcription factor *OTX2* (3%).³⁶ Enhancer hijacking events leading to the upregulation of *GFI1* and *GFI1B* are present in 15%–20% of group 3 medulloblastomas and may also be important driver events in this subgroup.³⁸ Cytogenetic events are abundant in this subgroup. Isochromosome 17q is present in 40%–50% of cases, and other common events are loss of chromosomes 8, 10q, and 16q and gain of 1q, 7, and 18.³⁶

Several subtype classifications for group 3 medulloblastoma have emerged. One study outlined high-risk and low-risk subtypes using methylation data, in which the high-risk subgroup featured frequent *MYC* amplifications in infants and a hypomethylation phenotype.⁵⁹ Another study defined three subtypes: 3 α (occurring in infants and frequently metastatic but associated with a better outcome), 3 β (occurring in older children and featuring *OTX2* gain, *DDX31* loss, and high *GFI1/GFI1B* expression), and 3 γ (occurring in infants and associated with high rates of metastasis and *MYC* amplification).⁷

Group 4

Group 4 medulloblastoma accounts for 35%–40% of all medulloblastoma diagnoses.⁶¹ It typically occurs in childhood and adolescents and far more frequently in males (3:1 sex ratio).⁶¹ Anatomically, these tumors typically have a midline vermian location.⁴⁶ Although this subgroup is

Risk Category	Low Risk	Standard Risk	High Risk	Very High Risk
Survival (%)	>90	75-90	50-75	<50
Subgroup, clinical and molecular characteristics	Non-metastatic	Non-metastatic, <i>TP53</i> WT and no <i>MYCN</i> amplification	One or both: • Metastatic • <i>MYCN</i> amplification	<i>TP53</i> Mutation
	Non-metastatic and Chromosome 11 loss	Non-metastatic and no <i>MYC</i> amplification	Metastatic	Metastatic
		Non-metastatic and no chromosome 11 loss		

FIG. 3. Proposed risk stratification for noninfant medulloblastoma, based on data from the following reference.⁵⁰ Box color represents the subgroup and the text reflects clinical and molecular criteria (WNT: blue, SHH: red, group 3: yellow, group 4: green). WT = wild type. Figure is available in color online only.

also frequently metastatic (35%–40% at diagnosis), survival outcomes are intermediate in this subgroup and recurrences tend to occur late.^{51,61}

The cell of origin of group 4 medulloblastoma has not been definitively established; however, these tumors appear to have transcriptional similarities to unipolar brush cells.⁶⁷ Common somatic mutations are also rare in this subgroup. *KDM6A*, *ZMYM3*, *KTM2C*, and *KBTBD4* are the most commonly mutated genes but occur in only 6%–9% of cases.³⁶ As in group 3 tumors, amplifications in *MYCN* and *OTX2* and enhancer hijacking–mediated overexpression of *GFI1* and *GFI1B* are recurrent driver events in group 4 tumors.³⁶ Other frequent events in this subgroup are *CDK6* amplification (6%) and overexpression of *PRDM6* via an enhancer hijacking event (17%), which frequently occurs with *SNCAIP* duplication events.³⁶ Cytogenetic events include isochromosome 17q, gain of chromosomes 7 and 18q, and loss of 8q, 8p, 11p, and X.^{36,61}

High-risk and low-risk subtypes were characterized by Schwalbe et al., in which the high-risk group was enriched for isochromosome 17q and had a 36% 10-year survival, whereas the low-risk group had chromosome 11 loss and a 72% 10-year survival.⁵⁹ Cavalli et al. subdivided group 4 tumors into three subtypes. Molecular features associated with these subtypes include *MYCN* and *CDK6* amplification in group 4 α , *SNCAIP* duplication in group 4 β , and *CDK6* amplification in group 4 γ .⁷

Risk Stratification

Prior to the identification of medulloblastoma subgroups, patient risk stratification for the purposes of treatment allocation and in clinical trial design divided patients into average-risk and high-risk groups.⁵⁰ This stratification system used age at diagnosis, metastatic stage, and extent of resection as the key criteria to determine the risk group. In this system, average-risk patients are those older than 3 years of age at diagnosis, without metastatic disease (M0 Chang stage), and with total or near-total resection (NTR; residual tumor volume < 1.5 cm³).^{18,41} Average-risk patients typically had 80% survival rates in contemporary

studies.⁴¹ Patients not meeting the aforementioned criteria were classified as high risk, with survival rates ranging from 60% to 65%.^{12,20}

Recently, an updated risk stratification proposal for medulloblastoma patients ages 3–17 was developed (Fig. 3), taking into account subgroup status and select genetic and cytogenetic aberrations to more accurately predict outcome.⁵⁰ This stratification system assigns patients to one of four risk groups: low risk (> 90% survival), standard risk (75%–90% survival), high risk (50%–75% survival), and very high risk (< 50% survival).⁵⁰

Treatment

Tumor Resection

The importance of tumor resection was recognized by Cushing, who noted an increased survival time in patients who had undergone radical resection versus biopsy alone.¹¹ The importance of the extent of resection has been revisited in observational studies over time, refining our understanding of how best to surgically manage these patients. These studies have generally demonstrated that NTR and gross-total resection (GTR) have similar outcomes, suggesting a general guiding principle of maximal safe resection.¹ Recently, the benefit of extent of resection was reanalyzed while controlling for the molecular subgroup in a cohort of 787 patients.⁶² After controlling for subgroup across the entire cohort, there was a progression-free survival (PFS) benefit with GTR over that with subtotal resection (STR; defined as residual tumor $\geq$ 1.5 cm³) but no benefit for PFS or overall survival (OS) with GTR over NTR (residual tumor < 1.5 cm³).⁶² In the analysis of PFS and OS for individual subgroups, only the patients with group 4 tumors appeared to have a PFS benefit with GTR over STR.⁶² To summarize, while GTR remains the ideal goal of surgery, similar outcomes can be expected in patients with minimal residual tumor, and surgeons must weigh the potential neurological morbidity of a more complete resection against leaving residual tumor. Of note, an important goal of surgery is obtaining sufficient tissue for histopathological diagnosis and molecular analysis. Given

the spatial molecular heterogeneity within the primary tumor, multiregional tissue sampling during resection, especially of regions of residual tumor, is important to determine the ubiquity of genetic and epigenetic aberrations, aiding in the rational selection of targeted therapy.

The role of resection for locally recurrent medulloblastoma has not been rigorously investigated. Studies have suggested a benefit to repeat resection; however, these studies tend to have highly selected patients, and analyses accounting for molecular subgroup are lacking.³ Nonetheless, given the divergent evolution and clonal selection that occur throughout therapy, biopsy or repeat resection of recurrent tumor may provide molecular insights to guide therapy for recurrence.³⁴

Radiation Therapy

In children older than 3–5 years of age, the current convention for radiotherapy involves radiation to the entire craniospinal axis in order to treat or provide prophylaxis against metastatic recurrence. Patients without metastatic disease who have had at least NTR of the primary tumor receive a 23.4-Gy dose of craniospinal radiation and a 54.0-Gy boost to the tumor bed.^{12,41,42} Radiation strategies for patients who present with metastatic disease are more variable, with patients in most North American centers receiving a 36.0-Gy dose of craniospinal radiation, with a 54.0-Gy dose to the primary tumor bed and a 50.0- to 54.0-Gy boost to nodular metastatic deposits.^{12,18} In Europe, patients with metastases often receive radiotherapy following chemotherapy, in either conventional (single dose per day) or hyperfractionated (two doses per day) regimens.¹⁴ Current areas of investigation are establishing the efficacy of treatment de-escalation for WNT medulloblastoma and incorporating alternate radiation technologies, such as proton beam therapy in place of photon-based radiation.⁷²

Chemotherapy

Current chemotherapy regimens are primarily determined by the patient's age, suitability for radiotherapy, and risk category. In children over 3–5 years old who receive radiation and have NTR or GTR and no metastases, the current standard of care proposed by the Children's Oncology Group (COG) is a chemotherapy regimen starting with weekly vincristine concurrent with radiotherapy, followed by eight cycles of cisplatin, vincristine, and either cyclophosphamide or lomustine.^{41,43} The optimal chemotherapy regimen in patients categorized as high risk in the nonmolecular risk stratification system has not been defined; thus, there is more variability in chosen agents and number of cycles. For example, a recent COG trial used carboplatin and vincristine during radiotherapy, followed by six cycles of cyclophosphamide and vincristine, with some patients also receiving cisplatin.¹⁸ Other trials have investigated the use of intraventricular methotrexate and high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT).⁶⁸ In young children (under the ages of 3–5), in whom the neurological impairment caused by radiotherapy precludes its use, multi-agent chemotherapy is used to delay the use of radiotherapy. As in older patients with high-risk disease, clinical trials have also

incorporated intrathecal methotrexate and high-dose myeloablative chemotherapy with autologous HCT for young children with medulloblastoma.⁵⁸

Side Effects of Therapy

Trade-offs between the side effects of current therapies and the potential improved survival have caused survival rates to be relatively stagnant over the past three decades.²⁰ Resection can be complicated by neurological deficits, particularly posterior fossa syndrome (cerebellar mutism), which occurs in approximately 25% of patients and characteristically manifests as difficulty with language production and emotional lability.²⁸ Radiotherapy and cytotoxic chemotherapy, particularly in younger children, are associated with neurocognitive impairment, hearing loss (potentially exacerbated by cisplatin chemotherapy), short stature, pituitary hormone deficiency, cataracts, cerebrovascular disease (e.g., stroke, intracranial hemorrhage, cavernous malformations), and secondary malignancies.^{18,53} These factors have significant impacts on the quality of life of medulloblastoma survivors and increase the urgency to identify more effective treatments to improve stagnant survival rates while also identifying therapies that reduce the long-term sequelae of current treatments.

Landscape of Current Clinical Trials

Many clinical trials currently underway have started to harness the insights provided by our improved understanding of the molecular underpinnings of medulloblastoma.

Treatment De-Escalation for WNT Medulloblastoma

Identification of the low-risk WNT subgroup spurred numerous trials investigating treatment de-escalation in children harboring these tumors, with the goals of reducing treatment-related toxicities, improving quality of life outcomes, and maintaining excellent survival rates. For example, clinical trials NCT02066220, NCT01878617, and NCT02724579 are studying reduced-dose craniospinal radiation and primary tumor bed boost in combination with reduced-dose chemotherapy. Another clinical trial, NCT02212574, investigating a treatment approach using chemotherapy and surgery without radiotherapy for these patients was suspended.

Incorporating Targeted Therapies for SHH Medulloblastoma

Inhibition of SHH signaling has long been recognized as a potential targeted therapy for medulloblastoma harboring genetic alterations in SHH pathway genes.^{30,55} Previous studies using vismodegib and sonidegib, competitive antagonists of the smoothened receptor, have demonstrated improved PFS in SHH medulloblastoma.^{5,30,55} Of note, many patients treated with SMO inhibition have developed treatment resistance over time, suggesting that monotherapy with these agents alone may be insufficient for durable remission. A proposed target downstream of SMO in the SHH pathway is CK2 inhibition, and a phase 1/2 trial using the CK2 inhibitor CX-4945 in recurrent SHH medulloblastoma is currently recruiting patients (NCT03904862).⁴⁹

FIG. 4. Key features of medulloblastoma metastasis, based on data from the following references.^{15,71} **A:** The primary tumor in the cerebellum is composed of distinct subclones, of which select clones may have metastatic potential. **B:** Metastatic clones may shed from the primary tumor into the CSF circulation or extravasate into local circulation. **C:** Metastatic cells transit via a CSF route or a hematogenous route to colonize distant leptomeningeal sites. **D:** Metastatic clones undergo further genetic divergence in the leptomeningeal niche and undergo complex interactions with the tumor microenvironment, including immune cell interaction and neovascularization. Copyright Azuravesta Design. Published with permission. Figure is available in color online only.

Stratifying Patients by Subgroup and Disease Risk

A multicenter trial currently underway (NCT01878617) provides a template for incorporating subgroup and risk stratification status into the trial design. The trial uses molecular subgroup (WNT, SHH, and non-WNT/non-SHH) and clinical and cytogenetic characteristics to stratify patients. Low-risk WNT patients receive reduced-intensity therapy, skeletally mature SHH patients receive vismodegib (in addition to standard of care treatment), and standard-risk and high-risk non-WNT/non-SHH patients are prioritized for treatment intensification with pemetrexed and gemcitabine.

Priorities for Preclinical Research

Improving Preclinical Models of Medulloblastoma

While several preclinical models of medulloblastoma are available, recent advances in the understanding of medulloblastoma cell of origin and molecular subtype may help to guide the development of novel models of this disease, particularly group 3 and group 4, for which existing models that recapitulate human disease are lacking.^{7,25,34,67} Understanding of the cell of origin may aid in driving key genetic aberrations in the appropriate cell type and developmental context in preclinical models. Attempting to model medulloblastoma subtypes, rather than subgroups, may provide the opportunity to model important driver events that are common in a particular subtype but rare at a subgroup level. Refinement of preclinical models in this way may improve the likelihood of successful translation while also guiding proper inclusion criteria for subsequent clinical trials.

Understanding Mechanisms of Recurrence and Treatment Resistance

Patients with recurrent medulloblastoma following current standard of care treatment have dismal outcomes, with survival rates under 10% despite aggressive treatment approaches including repeat resection, re-irradiation, and various high-dose chemotherapy regimens.^{3,13,21} Recent work has started to reveal the complexity of medulloblastoma recurrence. One important insight is that the medulloblastoma molecular subgroup remains unchanged at recurrence.³⁴ A limitation in studying disease recurrence to date is the limited number of available matched primary and recurrent patient samples, particularly for group 3 and 4 medulloblastomas, which tend to recur as distant metastases not amenable to resection or biopsy. Nonetheless, existing data have revealed that potentially actionable events in the primary tumor sample are often absent in recurrent tumor samples, suggesting that significant divergent evolution and clonal selection alter the drivers of tumorigenesis and maintenance in recurrence.³⁴ Given the lack of human data, this is a key area that can be addressed in preclinical models to better understand common mechanisms of treatment resistance and recurrence and to identify new treatment strategies.

Targeting Medulloblastoma Metastasis

Medulloblastoma metastasis, which almost universally disseminates to the leptomeninges (Fig. 4), is a poor prognostic marker in nearly all medulloblastoma patients, except those with WNT medulloblastoma, where metastasis is exceptionally rare.⁵⁰ Yet, little is known about the molecular programs necessary for medulloblastoma metastasis and survival in the leptomeningeal space, and there are no

FIG. 5. Proposed targeted therapies in specific molecular subgroups of medulloblastoma, based on data from the following references:^{4,10,19,27,29,33,45,49,55,65,73} Inhibition of SMO or CK2 in the SHH subgroup (A), targeting MYC-driven group 3 medulloblastoma using combination therapy with HDAC inhibitors and PI3K pathway inhibition (B) or BET-bromodomain inhibition to downregulate MYC expression (C), LSD1 inhibition in group 3 and group 4 medulloblastoma with *GFI1/GFI1B* overexpression (D), and CDK4/6 inhibition in non-WNT medulloblastoma (E). Copyright Azuravesta Design. Published with permission. Figure is available in color online only.

therapies that target this paramount clinical problem. Pre-clinical studies have demonstrated that metastatic medulloblastoma, like recurrent medulloblastoma, contains distinct molecular events compared to those of the primary tumor and have identified potential driver pathways, such as the PI3K signaling pathway.^{69,71} Another recent study has shed doubt on the dogma that medulloblastoma metastasizes to the leptomeninges exclusively via transit through the cerebrospinal fluid, suggesting a potential hematogenous route for metastatic spread.¹⁵ Investigations that further characterize the mechanisms of metastasis may provide rational treatment targets for this high-risk disease. Numerous emerging technologies will allow for characterization of the tumor microenvironment in the metastatic niche, providing insights into how tumor cell interactions with other cell types support survival in the leptomeningeal space.

Priorities for the Next Generation of Clinical Trials

Given the overall rarity of medulloblastoma combined with the ever-increasing refinement of the molecular stratification of this disease, great coordination and planning are required so that upcoming trials are designed to strategically leverage the wealth of knowledge that our molecular understanding of this disorder has provided. Trials should

incorporate not only subgroup information but also key genetic, cytogenetic, and epigenetic signatures that can predict outcome or suggest rational treatment targets. Additionally, trial outcomes must be carefully designed to effectively study this diverse disease entity. For example, the prospect of treatment de-escalation could be applied to the low-risk nonmetastatic group 4 tumors with chromosome 11 loss.⁵⁰ However, given that group 4 medulloblastoma can recur more than 5 years after initial diagnosis, such a study would require longer-term follow-up for appropriate survival analysis.⁵¹ High-risk subgroups and subtypes must be prioritized for treatment intensification given the urgent need to improve outcomes for these patients, such as SHH patients with *TP53* mutation and non-WNT patients with metastatic disease.⁵⁰ Numerous preclinical studies have identified potential strategies to implement for these high-risk patients, including combination therapy with PI3K pathway inhibitors and histone deacetylase inhibitors or BET-bromodomain inhibitors for MYC-driven group 3 medulloblastoma, targeting LSD1 in medulloblastoma with *GFI1/GFI1B* over-activation, CDK inhibitors, and cell cycle checkpoint inhibitors (Fig. 5).^{4,10,29,45} Given that metastatic disease is a key risk factor for treatment failure, the upfront addition of novel agents to current first-line treatments must be considered, rather than initiating these treatments after disease recurrence or progression. Trials of treatments for medul-

loblastoma recurrence incorporating precision medicine approaches must consider re-biopsy of the tumor to ensure the correct targeted agent is selected, especially given the temporal and spatial heterogeneity of medulloblastoma.^{34,71} Finally, quality of life should be carefully examined so that a more precise understanding of how new interventions are changing patient outcomes can be reached.

Acknowledgments

We thank Azuravesta Rastan (Azuravesta Biomedical Design) for assistance in the preparation and design of the figures in this paper.

Dr. Taylor is supported by the NIH (R01CA148699 and R01CA159859), Pediatric Brain Tumor Foundation, Terry Fox Research Institute, Canadian Institutes of Health Research, Cure-Search Foundation, b.r.a.i.n.child, Meagan's Walk, The Swifty Foundation, Genome Canada, Genome British Columbia, Genome Quebec, Ontario Research Fund, Worldwide Cancer Research, V Foundation for Cancer Research, and Ontario Institute for Cancer Research through funding provided by the Government of Ontario. Dr. Taylor is also supported by a Canadian Cancer Society Research Institute Impact grant and by a Stand Up To Cancer (SU2C) St. Baldrick's Pediatric Dream Team Translational Research Grant (SU2C-AACR-DT1113) and SU2C Canada Cancer Stem Cell Dream Team Research Funding (SU2C-AACR-DT-19-15) provided by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, with supplementary support from the Ontario Institute for Cancer Research through funding provided by the Government of Ontario. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. Dr. Taylor is also supported by the Garron Family Chair in Childhood Cancer Research at The Hospital for Sick Children and the University of Toronto. Dr. Juraschka is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarships, the University of Toronto Clinician Investigator Program, and the University of Toronto Surgeon-Scientist Training Program.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Taylor. Administrative/technical/material support: Taylor. Study supervision: Taylor.

Correspondence

Michael D. Taylor: The Hospital for Sick Children, Toronto, ON, Canada. mdtaylor@sickkids.ca.