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REVIEW

Medulloblastoma: experimental models and reality

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Abstract Medulloblastoma is the most frequent malignant brain tumor in childhood, but it may also affect infants, adolescents, and young adults. Recent advances in the understanding of the disease have shed light on molecular and clinical heterogeneity, which is now reflected in the updated WHO classification of brain tumors. At the same time, it is well accepted that preclinical research and clinical trials have to be subgroup-specific. Hence, valid models have to be generated specifically for every medulloblastoma subgroup to properly mimic molecular fingerprints, clinical features, and responsiveness to targeted therapies. This review summarizes the availability of experimental medulloblastoma models with a particular focus on how well these models reflect the actual disease subgroup. We further describe technical advantages and disadvantages of the models and finally point out how some models have successfully been used to introduce new drugs and why some medulloblastoma subgroups are extraordinary difficult to model.

Keywords Medulloblastoma · Mouse model · SHH · WNT · Group 3 · Group 4

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Heterogeneity in human medulloblastoma

For decades, medulloblastoma has been recognized as an extraordinarily heterogeneous disease, which per se challenges the generation of model systems. Histologically, pathologists can distinguish classic, desmoplastic, extensively nodular, and large cell/anaplastic variants of medulloblastoma. Strikingly, these histological features correlate with epidemiological and clinical aspects. In this sense, it became clear that desmoplastic or extensively nodular medulloblastoma occurs in infants, adolescents, or adults, and is associated with a slightly better prognosis [65]. On the other hand, large cell/anaplastic medulloblastoma that usually occurs in children exhibits a significantly more aggressive disease course [7].

First molecular analyses in the nineties of the last century have identified a subset of medulloblastoma with mutations in the Sonic hedgehog (SHH) signaling pathway, mostly, but not exclusively, in desmoplastic or extensively nodular medulloblastoma [55, 59]. Mutations in the WNT signaling pathway had been recognized in classical medulloblastoma [37, 85], and amplifications within *MYC* or *MYCN* had been detected in the large cell/anaplastic variants of medulloblastoma [2, 7]. Therefore, over time, it became obvious that there is also genetic heterogeneity, which, again, correlates with histology and clinical aspects.

The availability of high-throughput transcriptomic analyses revealed in 2002 that global gene expression might predict patients outcome [56], but it took some more time to detect that global gene expression might be used to identify several medulloblastoma subgroups that differ with respect to biology and clinical outcome [11, 39, 47, 76]. In deed, the correlation of such a classification with biological and clinical outcomes turned out to be superior to standard histology. The community quickly agreed on four molecular

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subgroups (WNT, SHH, Group 3, and Group 4; Fig. 1), with WNT medulloblastoma having the best and Group 3 medulloblastoma having the worst clinical prognoses [75]. Tumors of the different subgroups show distinct localizations within the hindbrain [81]. Later on, it could even be demonstrated that the analysis of global DNA methylation is an appropriate technique to determine the subgroup of a medulloblastoma [31, 32], with the important advantage of only needing small amounts of genomic DNA that may be extracted from archived formalin-fixed, paraffin-embedded tumor material.

The existence of four molecular subgroups is nowadays well accepted and begins to be incorporated in the design of clinical trials. However, high-throughput analyses point to clearly more heterogeneity than just four subgroups [9, 69]. Most obviously, SHH medulloblastomas split into infantile and adult cases that not only occur in different age groups, but display different transcriptomes, genomes, and epigenomes [38, 46]. In addition, there are a few childhood cases that arise in the setting of Li–Fraumeni syndrome or carry somatic *TP53* mutations [38]. Such tumors often have large cell/anaplastic histology and are associated with particularly poor outcome (Fig. 1), so that the WHO brain tumor classification has defined SHH MBs with *TP53* mutations as a separate subgroup.

While histology and genetics of medulloblastoma may change upon recurrence [45, 57], the dedication to one of the four molecular subgroups remains stable both in metastases as well as in recurrences [60, 80]. Subgroup specification is also spatially homogeneous within a single medulloblastoma tumor sample [44]. Conversely, somatic mutations display a huge spatial heterogeneity within one tumor sample, a phenomenon that has to be regarded as a big challenge in terms of targeted therapies [44].

Technical approaches to model medulloblastoma

The ideal medulloblastoma model should be most similar to its human counterpart concerning clinical features, the (histological) phenotype and biology. It should reflect the right cell of origin and exhibit the same genetic alterations, resulting in a tumor with a similar global transcriptomic or even epigenetic pattern. The model should enable efficient therapy screenings. Most importantly, the model should faithfully predict the tumor's responsiveness to selected therapies, even taking into account drug delivery across the blood brain barrier. None of the models that are currently available for medulloblastoma can cover all of these aspects. However, combining several models and tightly comparing results from model systems with human tumor material can provide important clues about the cell of origin, the pathogenesis, and possible treatment options. An overview on advantages and disadvantages of the major approaches to model medulloblastoma is given in Fig. 2.

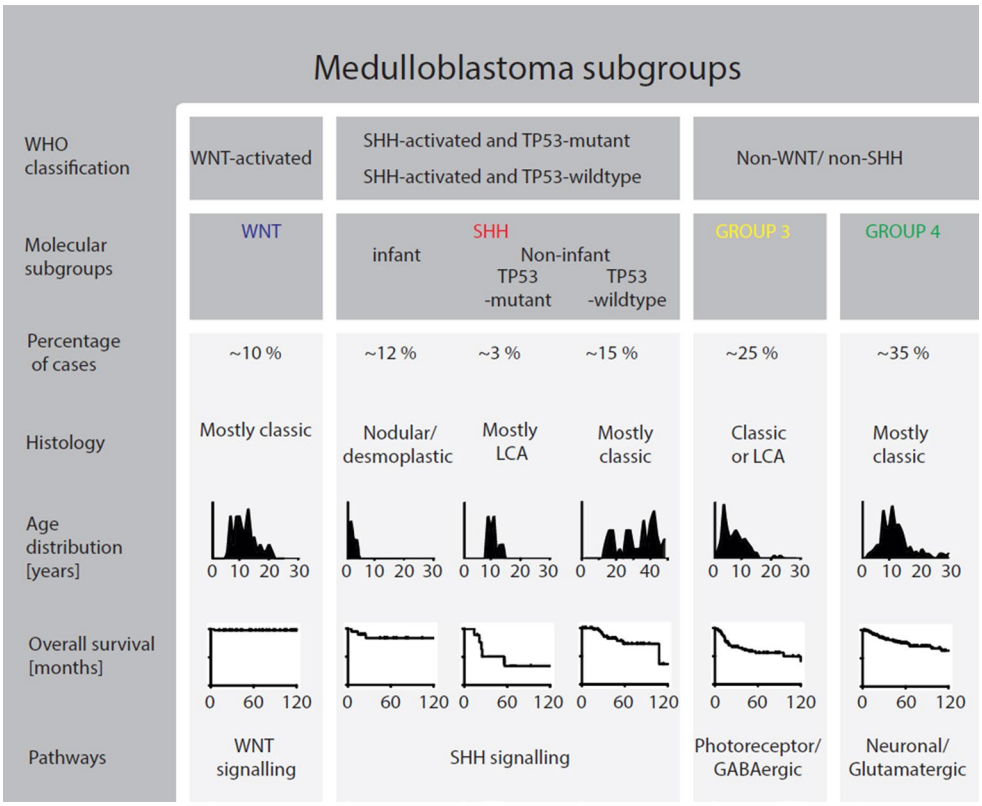


Fig. 1 Overview on human medulloblastoma subgroups

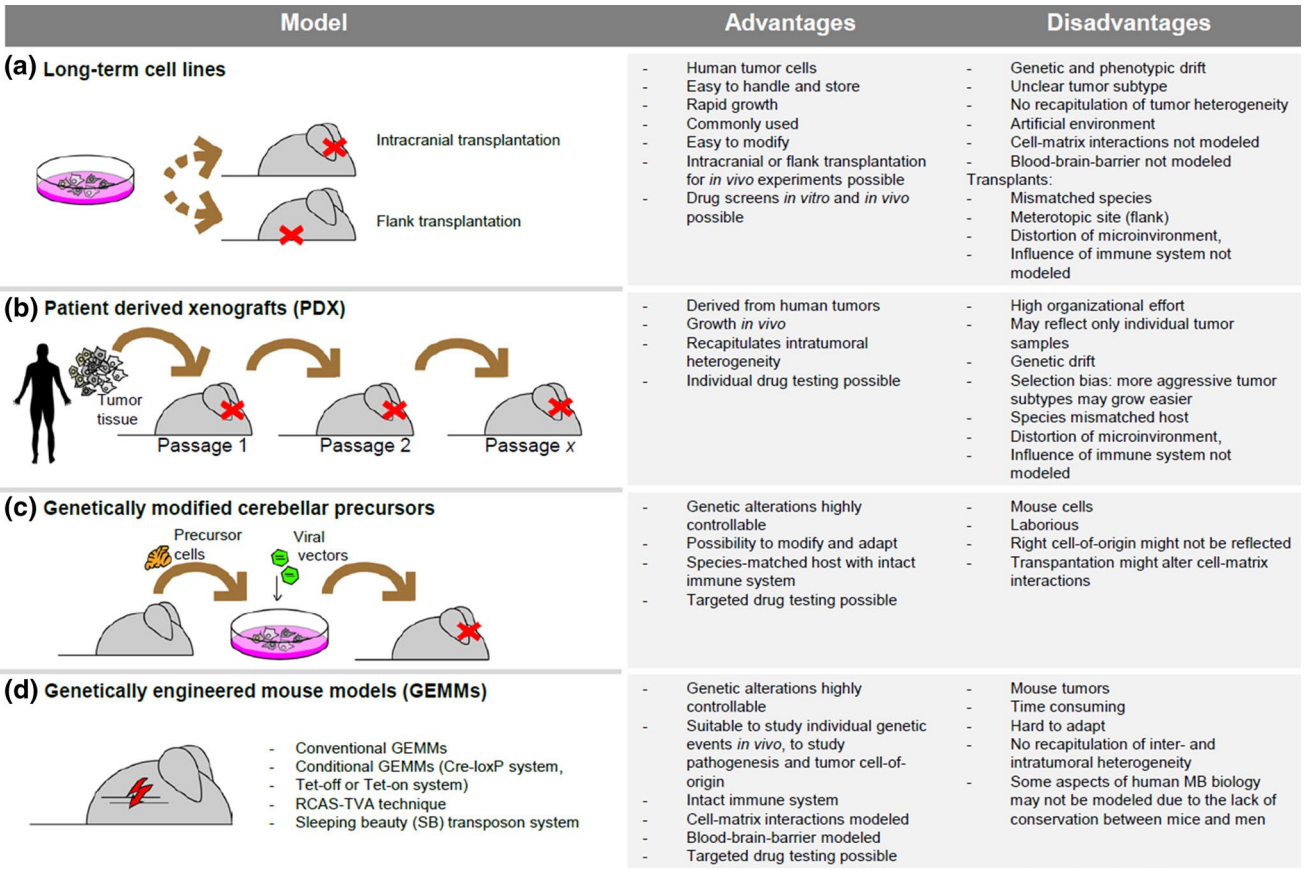


Fig. 2 Technical approaches to model medulloblastoma

The use of fresh human tumor material to learn about the biology of medulloblastoma cells and to screen for potent drugs has already been started in the 1980s and 1990s when the first permanent cell lines had been published [16, 17, 27, 34, 54]. These cell lines that are available until today usually grow in serum-containing medium and are very easy to handle. Most of them even grow in the brain or flank of host mice after appropriate transplantation (Fig. 2a). Molecular subgrouping has not been completed and properly compared to human counterparts for all cell lines [33], and available data are somewhat contradictory. The commonly used D283med cell line, for instance, has been assigned to Group 4 by some authors [71], but has been shown to have features of Group 3 tumors by others [14, 70]. Similarly, UW228 cells have first been seen as derived from an SHH tumor [77], but later results indicated an origin from a Group 3 tumor [50]. Even more astonishing, MED6 cells turned out to have a wild-type sequence for *CTNNB1,* although the original tumor mass harbored a *CTNNB1* mutation at codon 37 [50]. In addition, when looking at hierarchical clusterings from gene expression analyses, cell lines usually cluster together instead of spreading out within the group of medulloblastoma tumor samples, indicating that they are more similar to each other than to other medulloblastoma samples [77]. Similar data have been demonstrated for the expression of certain proteins [10], together leading to the assumption that permanent cell lines acquire additional mutations, change their epigenome, and adapt their global gene expression profile once they have been passaged several times in cell culture. While this is not surprising given that the establishment of some of the lines dates back to the 1980, this appears to be similarly true for freshly prepared murine medulloblastoma cells, e.g., for tumor cells from *Ptch1*$^{+/-}$ mice that spontaneously develop medulloblastoma due to a constitutively activated Sonic hedgehog signaling pathway [21]. Once *Ptch1*$^{+/-}$ medulloblastoma cells have been put into culture, they lose their Shh pathway activity and do not respond anymore to pharmaceutical inhibitors of the pathway [67]. Since such fundamental changes are only preventable by not keeping the cells in culture and by serially transplanting them directly from mouse to mouse, researchers have started to do so for dozens of human medulloblastoma samples, which is time-consuming and expensive, and may not work for less aggressive subgroups, e.g., WNT medulloblastoma (Fig. 2b). On the other hand, such patient-derived xenografts (PDX) have already helped

to understand the responsiveness of targeted therapies to medulloblastoma with specific mutations within the Sonic hedgehog signaling pathway [38, 66].

In other model systems, non-neoplastic murine cells are manipulated in cell culture, before they are transplanted back into new host mice to grow as tumors (Fig. 2c). These cells are usually not passaged as frequently or not even passaged at all, though artificial changes due to the ex vivo growth may neither be excluded. This technique has mostly been used with purified cerebellar granule neuron precursors [3, 36], but also with less well defined 'cerebellar neural stem cells' [52, 72].

One option to avoid any in vitro step is the generation of genetically engineered mouse models (GEMMs), which is the only system that allows the observation of tumor development from its cell of origin. Further advantages and disadvantages are listed in Fig. 2d. The first conventional knockout system was the *Ptch1*$^{+/-}$ model that was created by replacement of parts of exon 1 (including the putative start codon) and all of exon 2 of the *Patched1* gene with *lacZ* and a neomycin resistance gene by homologous recombination [21]. This model mimics patients with Gorlin–Goltz syndrome, who eventually develop medulloblastoma [24]. While *Ptch1*$^{-/-}$ mice do not survive, *Ptch1*$^{+/-}$ mice spontaneously lose their second *Ptch1* allele in single cells, which then results in clonal tumor formation. There are further medulloblastoma-prone syndromes in human patients with germline deletions of tumor suppressors, such as the Turcot syndrome with *APC* mutations and the Rubinstein–Taybi syndrome with *CREBBP* mutations. However, neither *Apc*$^{+/-}$ nor *Crebbp*$^{+/-}$ mice develop medulloblastoma. Similarly, the unique loss of *Sufu* or *Brca2* in mice does not result in the formation of medulloblastoma [15, 40], although respective germline defects in humans cause Gorlin–Goltz syndrome or Fanconi anemia, both conditions that predispose to medulloblastoma [49, 51]. While the *Ptch1*$^{+/-}$ model has been used extensively over the last 20 years to understand medulloblastoma and to find appropriate therapies, it is largely unclear, why this seemingly simple two-hit-model does not work for the other above-mentioned tumor suppressors. On the other hand, researchers have started to combine the mutant *Ptch1* allele with other mutants, e.g., *p53* [82] or *Igf2* [25] and have generated a plethora of (inducible) conditional knockout mice, mostly using the Cre-loxP technique. Here, the Cre recombinase enzyme specifically recognizes two lox (loci of recombination) sites within the mouse DNA, causes recombination between them, and results in a deletion of the genes between the two lox sites. Obviously, this technique may be used to delete tumor suppressor genes, such as *Patched1*. It may also be used to delete a *polyA* sequence—a functional stop of transcription—that has been cloned between two *loxP* sites upstream of a mutated oncogene, e.g., *SmoM2*. In this case, medulloblastoma arises due to the heterozygous expression of a mutant *Smoothened* allele after exposure of Cre recombinase to cerebellar granule neuron precursors [68]. Interestingly, this whole system may be inducible, so that the deletion of a tumor suppressor or the activation of an oncogene can be initiated by a drug at any given time point after fertilization. The most commonly used drug in the field is tamoxifen, which activates transport of the Cre recombinase protein from the cytoplasm to the nucleus, where it can actively function. While most of the conditional knockout mice aim to model SHH medulloblastoma, this technique also helped to generate a model for WNT medulloblastoma [20]. Finally, a conditional model for Group 3 medulloblastoma was created using the Tet system, where transcription is reversibly turned on or off in the presence of the antibiotic tetracycline or one of its derivates, e.g., doxycycline [22]. In this case, mice with expression of tetracycline transactivator (tTA) under the control of the *Glt1* promoter were intercrossed with transgenic mice expressing both Tet-responsive element (TRE)-*MYCN* and Tet-responsive element (TRE)-firefly luciferase from a bidirectional operator. In the absence of tetracycline, such mice rapidly develop medulloblastoma [74].

Sporadic mouse models of MB have also been developed using in vivo postnatal gene transfer with replication-competent avian leukosis virus subgroup A (ALV-A) splice acceptor (RCAS) vectors to deliver different combinations of oncogenes in a tissue-specific manner [19]. To this end, one or more RCAS vector-producing cell lines are injected into the brain of a transgenic mouse engineered to express the ALV-A receptor, TV-A, in neural stem cells under control of the *Nestin* promoter. When the RCAS retrovirus infects the respective TV-A-expressing cell, virus replication does not occur, but retroviral RNA is reverse-transcribed to generate a proviral DNA. This DNA then integrates into the host genome and the exogenous gene is expressed as a spliced message driven by the constitutive retroviral promoter long terminal repeat (LTR). RCAS-mediated delivery of *Myc*, insulin-like growth factor 1 (*Igf1*), Hepatocyte growth factor (*Hgf*), *Bcl2*, or *MycN,* in combination with Shh overexpression to *Nestin*-TV-A cells demonstrated tumor-promoting interaction between multiple molecular pathways [4–6, 61, 62].

Finally, the sleeping beauty (SB) transposon system has been used to help modeling medulloblastoma. In general, SB is a powerful tool for cancer gene discovery in mice [12]. In the presence of a transposase enzyme, the SB transposon is excised from genomic DNA and inserted throughout the genome at sites containing thymine-adenine dinucleotides. A transposon integration site present in the genome at a significantly high frequency is then called a common insertion site (CIS). Tumors can arise or accelerate if the transposon activates proto-oncogenes or inactivates tumor suppressor genes located at the integration sites (transposon insertion

mutagenesis). In the case of medulloblastoma modeling, SB transposase has been driven by the *Math1* promoter, which drives expression into cerebellar granule neuron precursors [28] that are a known cell of origin for SHH medulloblastoma [68]. However, breeding with mice transgenic for a concatemer of the T2/onc transposon only produced medulloblastoma on a $Ptch1^{+/-}$ background. In comparison to tumors from $Ptch1^{+/-}$ mice, tumors with additional SB-mediated alterations showed increased penetrance, decreased latency, and metastatic dissemination. Furthermore, tumor suppressors and oncogenes can be identified that drive tumor growth in addition to *Ptch1* [83].

WNT medulloblastoma

The only mouse model for WNT medulloblastoma has been generated in 2010 by Gibson and colleagues. This appears rather late, since the molecular biology of human WNT medulloblastoma appears relatively simple and has already been unraveled in the late 1990s: The vast majority of such tumors harbor *CTNNB1* mutations. Still, respective *Ctnnb1* alterations are obviously not sufficient to drive medulloblastoma in mice [20]. However, when combined with *p53* mutations (and this combination does exist in human medulloblastoma), such mice develop hindbrain tumors closely resembling human WNT medulloblastoma (Fig. 3). This model is a nice example, how GEMMs can be used not only to perform preclinical trials, but also to understand the pathogenesis of a given tumor. First, Gibson and colleagues found that WNT medulloblastomas develop from precursor cells of the dorsal brainstem, but not from the cerebellum. This matches to the fact that all human WNT medulloblastomas display brainstem contact (Fig. 3) [81]. Second, the group showed in a more recent paper that blood vessels within WNT medulloblastoma are aberrantly fenestrated and permit the accumulation of high levels of intra-tumoral chemotherapy and a robust therapeutic response [53]. This not only explains the good overall survival of patients with WNT medulloblastoma, but may also pave the way for therapeutic alterations of the vessels of other tumor types to make chemotherapy more efficient.

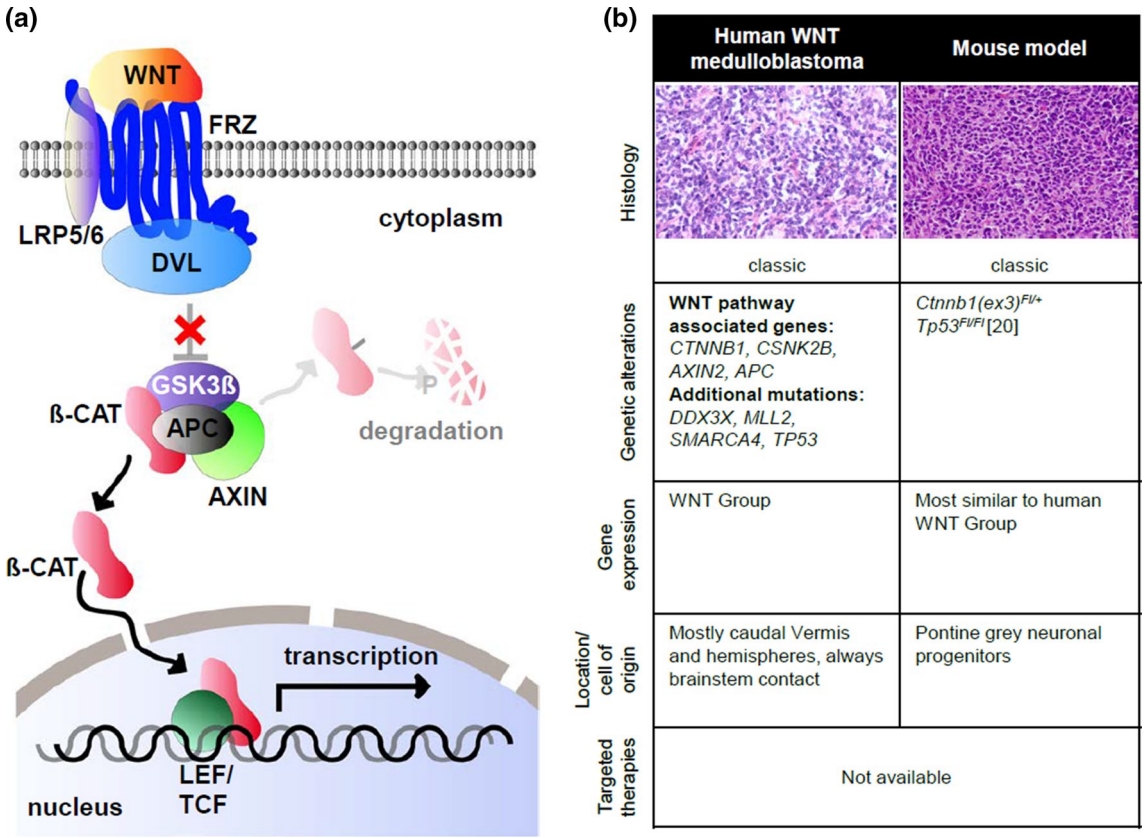
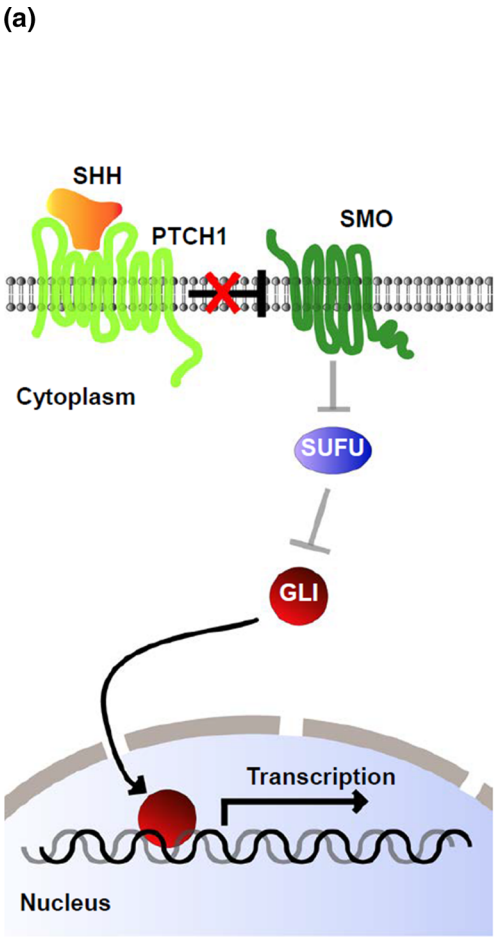


Fig. 3 WNT medulloblastoma. **a** Scheme of the active WNT pathway. **b** Comparison of available mouse models with human WNT medulloblastoma

SHH medulloblastoma

The number of experimental models for SHH medulloblastoma by far exceeds the number of models that exist for other subgroups of medulloblastoma. An overview comparing human SHH medulloblastoma and existing mouse models is given in Fig. 4. Most existing models are based on alteration in Ptch1 [21, 40, 78, 82, 84] or Smo [13, 23, 26, 68], which model mainly the adult variant of SHH medulloblastoma (Fig. 4). Depending on the model, tumor penetrance may be low, but may be altered by mouse radiation. While this facilitates some experiments, it may on the other hand appear artificial as radiation is not known as a cause for the growth of primary medulloblastoma. Models based on *Smo* mutations have shown that granule neuron precursors within the cerebellum and nucleus cochlearis serve as a tumor cell of origin—at least in mice [23, 68]. Other models that appear to model SHH medulloblastoma include mice with genetic changes in the interferon signaling [43, 79] as well as mice with DNA repair pathway mutations [30, 41]. However, the specific role of these alterations that were found to enhance medulloblastoma growth in mice is still unclear for human medulloblastoma.

In humans, these SHH tumors mainly grow in the cerebellar hemispheres, with some showing also brainstem contact [81]. Good models for medulloblastoma that are driven by mutations in downstream parts of the pathway, such as MycN, Gli1, Gli2, or Sufu, are lacking. *Sufu*$^{+/-}$ mice for instance, only develop medulloblastoma in combination with a Tp53 loss [40]. While *SUFU* mutations particularly occur in infants, *TP53* mutations are uncharacteristic in this patient group. Based on histology and gene expression, the respective mouse tumors actually rather match to human adult SHH medulloblastoma (Fig. 4) [40, 58]. Indeed, appropriate GEMMs for the infant subtype of SHH medulloblastoma are still missing. Similarly, medulloblastoma occurring in Li–Fraumeni patients with *TP53* germline mutations are not well modeled by GEMMs by now [58]. Nevertheless, the existing models for SHH medulloblastoma have already led to the development and testing of potent SHH inhibitors.



(b)

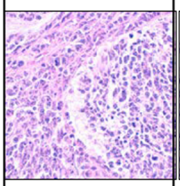
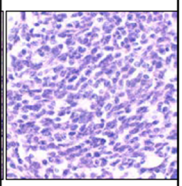
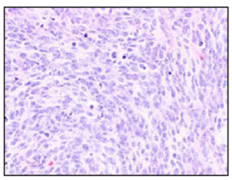
	Human SHH medulloblastoma: Infant	Human SHH medulloblastoma: Non-infant	Mouse models
Histology			
	Desmoplastic	Classic	Classic (*Ptch1*$^{+/-}$ model shown)
Genetic alterations	**SHH pathway associated genes:** *PTCH1, SUFU* **Additional mutations:** *BCOR, MDN1, FAT3, MLL2*	**SHH pathway associated genes:** *PTCH1, SMO, Gli2, MYCN* **Additional mutations:** *TP53, DDX3X, BRPF1, KIAA0182; NEB, CBP, TCF4*	**Knockin/Knockout/Transgenic:** *Ptch1*$^{+/-}$ [21], *Ptch1*$^{+/-}$*Trp53*$^{-/-}$ [82], *Ptch1*$^{+/-}$ *Cdkn2c*$^{-/-}$ [78], Sufu$^{+/-}$*Trp53*$^{-/-}$ [40] Cre-dependent *Ptch1*$^{Fl/Fl}$ [84] or dominant mutant *SmoM2*$^{Fl/+}$ (W539L) [23, 68] NeuroD2-driven dominant mutant *SmoA1* (W539L) [26] or SmoA2 (S537N) [13] **RCAS/TVA:** *Shh* with *Myc, Igf2,* activated *Akt (Akt-Myr-11–60), Bcl-2, Hgf, MycN,* or *MycN*^{T50A,S54A} [5, 6, 61, 62]
Gene expression	SHH subgroup, „infant"	SHH subgroup, „adult"	**Knockin/Knockout/Transgenic:** Most similar to human SHH subgroup, „adult"
Location/ cell of origin	Hindbrain midline structures and cerebellar hemispheres	Mostly rostral cerebellar hemispheres	Cerebellar granule neuron precursors, granule neurons of the cochlear nucleus
Targeted therapies	(Arsenic trioxide)	Vismodegib Sonidegib (Arsenic trioxide)	Arsenic trioxide, SMO inhibitors: Vismodegib (GDC-0449), Sonidegib (LDE-225), Saridegib (IPI-926) HhAntag, GANT61 HDAC1/HDAC2 inhibitors, PI-3K Inhibitors, Cyclopamine Itroconazole

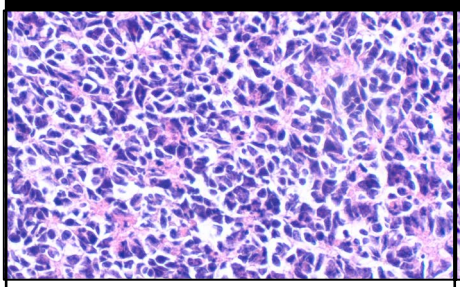
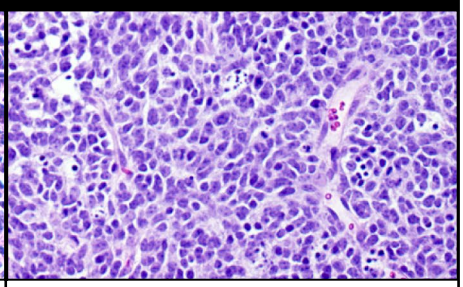
Fig. 4 SHH medulloblastoma. **a** Scheme of the active SHH pathway. **b** Comparison of available mouse models with human SHH medulloblastoma

Indeed, these inhibitors are—dependent on the genotype of the tumor—able to significantly inhibit medulloblastoma growth and have already made it into the clinics [63, 64]. This has to be regarded a good success, but various discrepancies between human and existing murine SHH medulloblastoma still have to be kept in mind. This is particularly true for the GEMMs, since PDX models appear to retain genome, epigenome, and transcriptome of the respective human case.

Group 3 medulloblastoma

There are a few available mouse models for Group 3 tumors (Fig. 5). Most models are MYC-driven and MYC is indeed commonly amplified and/or overexpressed in Group 3 tumors. Myc overexpression is insufficient in inducing medulloblastoma using the RCAS/TV-A system targeting Nestin-positive brain cells [18]. However, when combining Myc overexpression with overexpression of anti-apoptoic

Fig. 5 Comparison of available mouse models with human Group 3 medulloblastoma

	Human Group 3 medulloblastoma	Mouse model(s)
Histology		
	Anaplastic	Anaplastic (GTML tumor shown)
Genetic alterations	**MYC pathway associated genes:** *MYC, PVT1* **Additional mutations:** *OTX2, GFI1/1B, MLL2, SMARCA4, CTDNEP1, SPTB, LRP1B, TNXB, SNCAIP*	**Transgenic:** Glt1 driven MycN (GTML) [74] GTML and *Trp53*$^{KI/KI}$ (p53ER(TAM)) [29] RCAS/TVA: Myc + Bcl2 or Myc + Trp53$^{-/-}$ [35] **Transplanted genetically modified neural hindbrain precursors:** stabilized Myc (c-MycT58A) with dominant negative Trp53 (DNp53) [52] MSCV driven Myc, *in Cdkn2c*$^{-/-}$*Trp53*$^{-/-}$ cells [36] MSCV driven c-MycT58A and *Gfi1 or Gfi1b* [48]
Gene expression	Group 3	**Transgenic:** GTML: Most similar to Group 3. RCAS/TVA: Not described. **Transplanted genetically modified neural hindbrain precursors:** Often similar to Group 3 and sometimes to SHH
Location/ cell of origin	Mostly caudal Vermis, always brainstem contact	**Transgenic:** GTML: Develops in hindbrain, mostly extracerebellar, often brain stem or midbrain contact. RCAS/TVA: Cerebellar tumors from Nestin-positive cells. **Transplanted genetically modified neural hindbrain precursors:** - Postnatal cerebellar stem cells expressing Prominin-1 - Nestin-positive hindbrain cells - Cerebellar granule neuron precursors
Targeted therapies	Not yet available	BET inhibitors; Aurora Kinase Inhibitors, PI3K inhibitors, HDAC inhibitors, pemetrexed and gemcitabine

Bcl-2, large cell/anaplastic (LCA), Group 3 medulloblastoma is formed in Nestin-positive hindbrain cells [35].

Two groups reported that the MYC oncogene can be activated either in stem cells or in progenitor cells and can reprogram them into Group 3-like medulloblastoma. First, Pei et al. introduced Myc or a mutationally stabilized Myc (c-MycT58A) and dominant negative Trp53 (DNp53) in postnatal cerebellar stem cells expressing Prominin-1 (CD133), but lacking expression of lineage-specific markers defining cerebellar granule neuron precursors (CGNPs) [52]. While it has to be mentioned that primary medulloblastomas of Group 3 and 4 do not harbor *TP53* mutations, mice transplanted orthotopically developed embryonal tumors that resembled human LCA medulloblastoma and presented Group 3 tumor expression profiles. Second, Kawauchi et al. introduced Myc into CGNPs lacking p53 and p18 prior to orthotopic injection into mice [36]. Myc-induced tumors were distinct from WNT and SHH models showing Group 3 tumor resemblance. Interestingly, in infected CGNPs Myc is suppressing Math1, and transformed cells show increased levels of Prominin1 and other stem cell factors [36].

Wild-type MYCN can also promote Group 3 medulloblastoma development when overexpressed from the Glutamate transporter 1 (Glt1) promoter in the Glt1-tTA;TRE-MYCN/Luciferase (GTML) transgenic model [74]. Interestingly, when turning MYCN off in this Tet-OFF regulatable model, mice are completely cured, suggesting that tumors are dependent on the MYCN oncogene. Tumors induced in the GTML model closely resemble Group 3 medulloblastoma (Fig. 5), but also smaller sets of WNT, SHH, and Group 4 tumors arise, suggesting that MYCN can initiate and drive various types of medulloblastoma [29, 58, 73]. Crossing these animals to p53 depleted mice accelerates tumor formation, and as p53 is often found mutated in MB recurrences, these mice can probably be used for modeling and for better understanding of tumor relapse [29].

In some Group 3 (and Group 4) patients oncogenic activation of growth factor-independent 1 (GFI1) and GFI1B is initiated when these genes translocate themselves next to super-enhancers by the so-called 'enhancer-hijacking' [48]. These transcriptional repressors cannot promote tumor growth alone, but when coexpressed with Myc in neural stem cells, orthotopic transplantation into mice drives aggressive and metastatic Group 3 medulloblastoma.

The transcription factor orthodendrite homeobox 2 (OTX2) is frequently amplified in Group 3 and Group 4 medulloblastoma and is important in maintaining these tumors [1]. OTX2 directly binds to the promoter region of MYC [1] and has a high affinity to bind in proximity of MYC to distinct promoter regions [8]. However, OTX2 cannot drive brain tumor formation alone. These findings might disclose its importance in collaborating with MYC in Group 3 tumor formation and progression. Despite the obvious importance of OTX2 in Group 3 tumor biology, there are yet no good animal models for modeling OTX2-driven medulloblastoma.

Group 4 medulloblastoma

Apart from permanent cell lines and PDX models, there are no models available for Group 4 medulloblastoma, and the reason for this dramatic lack is clearly the rudimental understanding of the biology of Group 4 medulloblastoma. Among the few drivers that have recurrently been identified in Group 4 medulloblastoma, alterations of *MYCN* and structural variants that result in a pathological activity of *GFI1* or *GFI1B* have been modeled and resulted in the formation of medulloblastoma [48, 74]. However, thorough analysis has revealed that tumors arising in *Glt1-tTA;TRE-MYCN/Luc* mice more closely resemble Group 3 medulloblastoma [58]. Similarly, medulloblastoma arising in mice that have been orthotopically injected with neural stem cells transduced with viruses encoding for *GFI1* or *GFI1B* and *MYC* display and expression signature consistent with human Group 3 medulloblastoma [48].

Some MYCN-driven GTML tumors and brain tumors driven from postnatal and not embryonic hindbrain neural stem cells show a resemblance to Group 4 medulloblastoma [73]. However, as these tumors are either rare or still show many markers connected to SHH tumors, they cannot be used as reliable Group 4 models. Lin et al. recently described a regulatory enhancer landscape in a set of human medulloblastoma samples [42]. Here, important Group 4 regulators were identified including LMX1A, EOMES, and LHX2; active enhancers that could be useful when generating new Group 4 models.

Conclusions

Researchers have developed a number of good medulloblastoma models that resemble the human disease to a high degree. However, the more scientists identify biological heterogeneity in human medulloblastoma, the higher is the need to adapt the models and develop them further. Still, good progress has been made when it comes to the understanding of the biology of the disease (e.g., its cellular origin) or to the option to preclinically test SHH inhibitors. The biggest lack is still a reliable model for Group 4 medulloblastoma, which is the most frequent subgroup seen in patients, as well as models that are suitable to study medulloblastoma recurrences or a metastasizing disease.

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References

1. Adamson DC, Shi Q, Wortham M, Northcott PA, Di C, Duncan CG, Li J, McLendon RE, Bigner DD, Taylor MD et al (2010) OTX2 is critical for the maintenance and progression of Shh-independent medulloblastomas. Cancer Res 70:181–191. doi:10.1158/0008-5472
2. Aldosari N, Bigner SH, Burger PC, Becker L, Kepner JL, Friedman HS, McLendon RE (2002) MYCC and MYCN oncogene amplification in medulloblastoma. A fluorescence in situ hybridization study on paraffin sections from the Children's Oncology Group. Arch Pathol Lab Med 126:540–544. doi:10.1043/0003-9985(2002)126
3. Ayrault O, Zhao H, Zindy F, Qu C, Sherr CJ, Roussel MF (2010) Atoh1 inhibits neuronal differentiation and collaborates with Gli1 to generate medulloblastoma-initiating cells. Cancer Res 70:5618–5627. doi:10.1158/0008-5472
4. Ben Arie N, Bellen HJ, Armstrong DL, McCall AE, Gordadze PR, Guo Q, Matzuk MM, Zoghbi HY (1997) Math1 is essential for genesis of cerebellar granule neurons. Nature 390:169–172
5. Binning MJ, Niazi T, Pedone CA, Lal B, Eberhart CG, Kim KJ, Laterra J, Fults DW (2008) Hepatocyte growth factor and sonic Hedgehog expression in cerebellar neural progenitor cells costimulate medulloblastoma initiation and growth. Cancer Res 68:7838–7845. doi:10.1158/0008-5472
6. Browd SR, Kenney AM, Gottfried ON, Yoon JW, Walterhouse D, Pedone CA, Fults DW (2006) N-myc can substitute for insulin-like growth factor signaling in a mouse model of sonic hedgehog-induced medulloblastoma. Cancer Res 66:2666–2672. doi:10.1158/0008-5472
7. Brown HG, Kepner JL, Perlman EJ, Friedman HS, Strother DR, Duffner PK, Kun LE, Goldthwaite PT, Burger PC (2000) "Large cell/anaplastic" medulloblastomas: a Pediatric Oncology Group Study. J Neuropathol Exp Neurol 59:857–865
8. Bunt J, Hasselt NE, Zwijnenburg DA, Koster J, Versteeg R, Kool M (2011) Joint binding of OTX2 and MYC in promotor regions is associated with high gene expression in medulloblastoma. PLoS One 6:e26058. doi:10.1371/journal.pone.0026058
9. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS et al (2017) Intertumoral heterogeneity within medulloblastoma subgroups. Cancer Cell 31(737–754):e736. doi:10.1016/j.ccell.2017.05.005
10. Chlapek P, Zitterbart K, Kren L, Filipova L, Sterba J, Veselska R (2017) Uniformity under in vitro conditions: changes in the phenotype of cancer cell lines derived from different medulloblastoma subgroups. PLoS One 12:e0172552. doi:10.1371/journal.pone.0172552
11. Cho Y-J, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, Berhoukim R, Amani V, Goumnerova L, Eberhart CG et al (2011) Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol 29:1424–1430
12. Collier LS, Largaespada DA (2005) Hopping around the tumor genome: transposons for cancer gene discovery. Cancer Res 65:9607–9610. doi:10.1158/0008-5472
13. Dey J, Ditzler S, Knoblaugh SE, Hatton BA, Schelter JM, Cleary MA, Mecham B, Rorke-Adams LB, Olson JM (2012) A distinct Smoothened mutation causes severe cerebellar developmental defects and medulloblastoma in a novel transgenic mouse model. Mol Cell Biol 32:4104–4115. doi:10.1128/MCB.00862-12
14. Fiaschetti G, Castelletti D, Zoller S, Schramm A, Schroeder C, Nagaishi M, Stearns D, Mittelbronn M, Eggert A, Westermann F et al (2011) Bone morphogenetic protein-7 is a MYC target with prosurvival functions in childhood medulloblastoma. Oncogene 30:2823–2835. doi:10.1038/onc.2011.10
15. Frappart PO, Lee Y, Lamont J, McKinnon PJ (2007) BRCA2 is required for neurogenesis and suppression of medulloblastoma. EMBO J 26:2732–2742. doi:10.1038/sj.emboj.7601703
16. Friedman HS, Burger PC, Bigner SH, Trojanowski JQ, Brodeur GM, He XM, Wikstrand CJ, Kurtzberg J, Berens ME, Halperin EC (1988) Phenotypic and genotypic analysis of a human medulloblastoma cell line and transplantable xenograft (D341 Med) demonstrating amplification of c-myc. Am J Pathol 130:472–484
17. Friedman HS, Burger PC, Bigner SH, Trojanowski JQ, Wikstrand CJ, Halperin EC, Bigner DD (1985) Establishment and characterization of the human medulloblastoma cell line and transplantable xenograft D283 Med. J Neuropathol Exp Neurol 44:592–605
18. Fults D, Pedone C, Dai C, Holland EC (2002) MYC expression promotes the proliferation of neural progenitor cells in culture and in vivo. Neoplasia 4:32–39. doi:10.1038/sj/neo/7900200
19. Fults DW (2005) Modeling medulloblastoma with genetically engineered mice. Neurosurg Focus 19:E7
20. Gibson P, Tong Y, Robinson G, Thompson MC, Currle DS, Eden C, Kranenburg TA, Hogg T, Poppleton H, Martin J et al (2010) Subtypes of medulloblastoma have distinct developmental origins. Nature 468:1095–1099
21. Goodrich LV, Milenkovic L, Higgins KM, Scott MP (1997) Altered neural cell fates and medulloblastoma in mouse patched mutants. Science 277:1109–1113
22. Gossen M, Bujard H (1992) Tight control of gene expression in mammalian cells by tetracycline-responsive promoters. Proc Natl Acad Sci USA 89:5547–5551
23. Grammel D, Warmuth-Metz M, von Bueren AO, Kool M, Pietsch T, Kretzschmar HA, Rowitch DH, Rutkowski S, Pfister SM, Schüller U (2012) Sonic hedgehog-associated medulloblastoma arising from the cochlear nuclei of the brainstem. Acta Neuropathol 123:601–614. doi:10.1007/s00401-012-0961-0
24. Hahn H, Wicking C, Zaphiropoulous PG, Gailani MR, Shanley S, Chidambaram A, Vorechovsky I, Holmberg E, Unden AB, Gillies S et al (1996) Mutations of the human homolog of *Drosophila* patched in the nevoid basal cell carcinoma syndrome. Cell 85:841–851
25. Hahn H, Wojnowski L, Specht K, Kappler R, Calzada-Wack J, Potter D, Zimmer A, Muller U, Samson E, Quintanilla-Martinez L et al (2000) Patched target Igf2 is indispensable for the formation of medulloblastoma and rhabdomyosarcoma. J Biol Chem 275:28341–28344. doi:10.1074/jbc.C000352200
26. Hallahan AR, Pritchard JI, Hansen S, Benson M, Stoeck J, Hatton BA, Russell TL, Ellenbogen RG, Bernstein ID, Beachy PA et al (2004) The SmoA1 mouse model reveals that notch signaling is critical for the growth and survival of sonic hedgehog-induced medulloblastomas. Cancer Res 64:7794–7800
27. He XM, Wikstrand CJ, Friedman HS, Bigner SH, Pleasure S, Trojanowski JQ, Bigner DD (1991) Differentiation characteristics of newly established medulloblastoma cell lines (D384 Med, D425 Med, and D458 Med) and their transplantable xenografts. Lab Invest 64:833–843
28. Helms AW, Abney AL, Ben-Arie N, Zoghbi HY, Johnson JE (2000) Autoregulation and multiple enhancers control Math1 expression in the developing nervous system. Development 127:1185–1196
29. Hill RM, Kuijper S, Lindsey JC, Petrie K, Schwalbe EC, Barker K, Boult JK, Williamson D, Ahmad Z, Hallsworth A et al (2015) Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. Cancer Cell 27:72–84. doi:10.1016/j.ccell.2014.11.002

30. Holcomb VB, Vogel H, Marple T, Kornegay RW, Hasty P (2006) Ku80 and p53 suppress medulloblastoma that arise independent of Rag-1-induced DSBs. Oncogene 25:7159–7165. doi:10.1038/sj.onc.1209704
31. Hovestadt V, Jones DT, Picelli S, Wang W, Kool M, Northcott PA, Sultan M, Stachurski K, Ryzhova M, Warnatz HJ et al (2014) Decoding the regulatory landscape of medulloblastoma using DNA methylation sequencing. Nature 510:537–541. doi:10.1038/nature13268
32. Hovestadt V, Remke M, Kool M, Pietsch T, Northcott PA, Fischer R, Cavalli FM, Ramaswamy V, Zapatka M, Reifenberger G et al (2013) Robust molecular subgrouping and copy-number profiling of medulloblastoma from small amounts of archival tumour material using high-density DNA methylation arrays. Acta Neuropathol 125:913–916. doi:10.1007/s00401-013-1126-5
33. Ivanov DP, Coyle B, Walker DA, Grabowska AM (2016) In vitro models of medulloblastoma: choosing the right tool for the job. J Biotechnol 236:10–25. doi:10.1016/j.jbiotec.2016.07.028
34. Jacobsen PF, Jenkyn DJ, Papadimitriou JM (1985) Establishment of a human medulloblastoma cell line and its heterotransplantation into nude mice. J Neuropathol Exp Neurol 44:472–485
35. Jenkins NC, Rao G, Eberhart CG, Pedone CA, Dubuc AM, Fults DW (2016) Somatic cell transfer of c-Myc and Bcl-2 induces large-cell anaplastic medulloblastomas in mice. J Neurooncol 126:415–424. doi:10.1007/s11060-015-1985-9
36. Kawauchi D, Robinson G, Uziel T, Gibson P, Rehg J, Gao C, Finkelstein D, Qu C, Pounds S, Ellison DW et al (2012) A mouse model of the most aggressive subgroup of human medulloblastoma. Cancer Cell 21:168–180. doi:10.1016/j.ccr.2011.12.023
37. Koch A, Waha A, Tonn JC, Sörensen N, Berthold F, Wolter M, Reifenberger J, Hartmann W, Friedl W, Reifenberger G et al (2001) Somatic mutations of WNT/wingless signaling pathway components in primitive neuroectodermal tumors. Int J Cancer 93:445–449
38. Kool M, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, Piro RM, Esparza LA, Markant SL, Remke M et al (2014) Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell 25:393–405. doi:10.1016/j.ccr.2014.02.004
39. Kool M, Koster J, Bunt J, Hasselt NE, Lakeman A, van Sluis P, Troost D, Meeteren NS, Caron HN, Cloos J et al (2008) Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. PLoS One 3:e3088
40. Lee Y, Kawagoe R, Sasai K, Li Y, Russell HR, Curran T, McKinnon PJ (2007) Loss of suppressor-of-fused function promotes tumorigenesis. Oncogene 26:6442–6447 **(pii:1210467)**
41. Lee Y, McKinnon PJ (2002) DNA ligase IV suppresses medulloblastoma formation. Cancer Res 62:6395–6399
42. Lin CY, Erkek S, Tong Y, Yin L, Federation AJ, Zapatka M, Haldipur P, Kawauchi D, Risch T, Warnatz HJ et al (2016) Active medulloblastoma enhancers reveal subgroup-specific cellular origins. Nature 530:57–62. doi:10.1038/nature16546
43. Lin W, Kemper A, McCarthy KD, Pytel P, Wang JP, Campbell IL, Utset MF, Popko B (2004) Interferon-gamma induced medulloblastoma in the developing cerebellum. J Neurosci 24:10074–10083. doi:10.1523/JNEUROSCI.2604-04.2004
44. Morrissy AS, Cavalli FMG, Remke M, Ramaswamy V, Shih DJH, Holgado BL, Farooq H, Donovan LK, Garzia L, Agnihotri S et al (2017) Spatial heterogeneity in medulloblastoma. Nat Genet. doi:10.1038/ng.3838
45. Morrissy AS, Garzia L, Shih DJ, Zuyderduyn S, Huang X, Skowron P, Remke M, Cavalli FM, Ramaswamy V, Lindsay PE et al (2016) Divergent clonal selection dominates medulloblastoma at recurrence. Nature 529:351–357. doi:10.1038/nature16478
46. Northcott PA, Hielscher T, Dubuc A, Mack S, Shih D, Remke M, Al-Halabi H, Albrecht S, Jabado N, Eberhart CG et al (2011) Pediatric and adult sonic hedgehog medulloblastomas are clinically and molecularly distinct. Acta Neuropathol 122:231–240. doi:10.1007/s00401-011-0846-7
47. Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P et al (2011) Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 29:1408–1414. doi:10.1200/JCO.2009.27.4324
48. Northcott PA, Lee C, Zichner T, Stutz AM, Erkek S, Kawauchi D, Shih DJ, Hovestadt V, Zapatka M, Sturm D et al (2014) Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature 511:428–434. doi:10.1038/nature13379
49. Offit K, Levran O, Mullaney B, Mah K, Nafa K, Batish SD, Diotti R, Schneider H, Deffenbaugh A, Scholl T et al (2003) Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 95:1548–1551
50. Othman RT, Kimishi I, Bradshaw TD, Storer LC, Korshunov A, Pfister SM, Grundy RG, Kerr ID, Coyle B (2014) Overcoming multiple drug resistance mechanisms in medulloblastoma. Acta Neuropathol Commun 2:57. doi:10.1186/2051-5960-2-57
51. Pastorino L, Ghiorzo P, Nasti S, Battistuzzi L, Cusano R, Marzocchi C, Garre ML, Clementi M, Scarra GB (2009) Identification of a SUFU germline mutation in a family with Gorlin syndrome. Am J Med Genet A 149A:1539–1543. doi:10.1002/ajmg.a.32944
52. Pei Y, Moore CE, Wang J, Tewari AK, Eroshkin A, Cho YJ, Witt H, Korshunov A, Read TA, Sun JL et al (2012) An animal model of MYC-driven medulloblastoma. Cancer Cell 21:155–167. doi:10.1016/j.ccr.2011.12.021
53. Phoenix TN, Patmore DM, Boop S, Boulos N, Jacus MO, Patel YT, Roussel MF, Finkelstein D, Goumnerova L, Perreault S et al (2016) Medulloblastoma genotype dictates blood brain barrier phenotype. Cancer Cell 29:508–522. doi:10.1016/j.ccell.2016.03.002
54. Pietsch T, Scharmann T, Fonatsch C, Schmidt D, Ockler R, Freihoff D, Albrecht S, Wiestler OD, Zeltzer P, Riehm H (1994) Characterization of five new cell lines derived from human primitive neuroectodermal tumors of the central nervous system. Cancer Res 54:3278–3287
55. Pietsch T, Waha A, Koch A, Kraus J, Albrecht S, Tonn J, Sörensen N, Berthold F, Henk B, Schmandt N et al (1997) Medulloblastomas of the desmoplastic variant carry mutations of the human homologue of *Drosophila* patched. Cancer Res 57:2085–2088
56. Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, Kim JY, Goumnerova LC, Black PM, Lau C et al (2002) Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature 415:436–442
57. Pöschl J, Koch A, Schüller U (2015) Histological subtype of medulloblastoma frequently changes upon recurrence. Acta Neuropathol 129:459–461. doi:10.1007/s00401-015-1397-0
58. Pöschl J, Stark S, Neumann P, Grobner S, Kawauchi D, Jones DT, Northcott PA, Lichter P, Pfister SM, Kool M et al (2014) Genomic and transcriptomic analyses match medulloblastoma mouse models to their human counterparts. Acta Neuropathol 128:123–136. doi:10.1007/s00401-014-1297-8
59. Raffel C, Jenkins RB, Frederick L, Hebrink D, Alderete B, Fults DW, James CD (1997) Sporadic medulloblastomas contain PTCH mutations. Cancer Res 57:842–845
60. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, Shih DJ, Luu B, Dubuc AM, Northcott PA et al (2013) Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol 14:1200–1207. doi:10.1016/S1470-2045(13)70449-2
61. Rao G, Pedone CA, Coffin CM, Holland EC, Fults DW (2003) c-Myc enhances sonic hedgehog-induced medulloblastoma

formation from nestin-expressing neural progenitors in mice. Neoplasia 5:198–204
62. Rao G, Pedone CA, Valle LD, Reiss K, Holland EC, Fults DW (2004) Sonic hedgehog and insulin-like growth factor signaling synergize to induce medulloblastoma formation from nestin-expressing neural progenitors in mice. Oncogene 23(36):6156–6162
63. Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, Packer RJ, Goldman S, Prados MD, Desjardins A et al (2015) 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 33:2646–2654. doi:10.1200/JCO.2014.60.1591
64. Rudin CM, Hann CL, Laterra J, Yauch RL, Callahan CA, Fu L, Holcomb T, Stinson J, Gould SE, Coleman B et al (2009) Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med 361:1173–1178 **(pii:NEJMoa0902903)**
65. Rutkowski S, Bode U, Deinlein F, Ottensmeier H, Warmuth-Metz M, Sörensen N, Graf N, Emser A, Pietsch T, Wolff JE et al (2005) Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 352:978–986
66. Sanden E, Dyberg C, Krona C, Gallo-Oller G, Olsen TK, Enriquez Perez J, Wickstrom M, Estekizadeh A, Kool M, Visse E et al (2017) Establishment and characterization of an orthotopic patient-derived Group 3 medulloblastoma model for preclinical drug evaluation. Sci Rep 7:46366. doi:10.1038/srep46366
67. Sasai K, Romer JT, Lee Y, Finkelstein D, Fuller C, McKinnon PJ, Curran T (2006) Shh pathway activity is down-regulated in cultured medulloblastoma cells: implications for preclinical studies. Cancer Res 66:4215–4222. doi:10.1158/0008-5472
68. Schüller U, Heine VM, Mao J, Kho AT, Dillon AK, Han YG, Huillard E, Sun T, Ligon AH, Qian Y et al (2008) Acquisition of granule neuron precursor identity is a critical determinant of progenitor cell competence to form Shh-induced medulloblastoma. Cancer Cell 14:123–134
69. Schwalbe EC, Lindsey JC, Nakjang S, Crosier S, Smith AJ, Hicks D, Rafiee G, Hill RM, Iliasova A, Stone T et al (2017) Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. Lancet Oncol. doi:10.1016/S1470-2045(17)30243-7
70. Sengupta S, Weeraratne SD, Sun H, Phallen J, Rallapalli SK, Teider N, Kosaras B, Amani V, Pierre-Francois J, Tang Y et al (2014) alpha5-GABAA receptors negatively regulate MYC-amplified medulloblastoma growth. Acta Neuropathol 127:593–603. doi:10.1007/s00401-013-1205-7
71. Snuderl M, Batista A, Kirkpatrick ND, Ruiz de Almodovar C, Riedemann L, Walsh EC, Anolik R, Huang Y, Martin JD, Kamoun W et al (2013) Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. Cell 152:1065–1076. doi:10.1016/j.cell.2013.01.036
72. Sutter R, Shakhova O, Bhagat H, Behesti H, Sutter C, Penkar S, Santuccione A, Bernays R, Heppner FL, Schüller U et al (2010) Cerebellar stem cells act as medulloblastoma-initiating cells in a mouse model and a neural stem cell signature characterizes a subset of human medulloblastomas. Oncogene 29:1845–1856 **(pii:onc2009472)**
73. Swartling FJ, Savov V, Persson AI, Chen J, Hackett CS, Northcott PA, Grimmer MR, Lau J, Chesler L, Perry A et al (2012) Distinct neural stem cell populations give rise to disparate brain tumors in response to N-MYC. Cancer Cell 21:601–613. doi:10.1016/j.ccr.2012.04.012
74. Swartling FJ, Grimmer MR, Hackett CS, Northcott PA, Fan QW, Goldenberg DD, Lau J, Masic S, Nguyen K, Yakovenko S et al (2010) Pleiotropic role for MYCN in medulloblastoma. Genes Dev 24:1059–1072. doi:10.1101/gad.1907510
75. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A et al (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123:465–472. doi:10.1007/s00401-011-0922-z
76. Thompson MC, Fuller C, Hogg TL, Dalton J, Finkelstein D, Lau CC, Chintagumpala M, Adesina A, Ashley DM, Kellie SJ et al (2006) Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol 24:1924–1931
77. Triscott J, Lee C, Foster C, Manoranjan B, Pambid MR, Berns R, Fotovati A, Venugopal C, O'Halloran K, Narendran A et al (2013) Personalizing the treatment of pediatric medulloblastoma: polo-like kinase 1 as a molecular target in high-risk children. Cancer Res 73:6734–6744. doi:10.1158/0008-5472.CAN-12-4331
78. Uziel T, Zindy F, Xie S, Lee Y, Forget A, Magdaleno S, Rehg JE, Calabrese C, Solecki D, Eberhart CG et al (2005) The tumor suppressors Ink4c and p53 collaborate independently with patched to suppress medulloblastoma formation. Genes Dev 19:2656–2667 **(pii:gad.1368605)**
79. Wang J, Pham-Mitchell N, Schindler C, Campbell IL (2003) Dysregulated Sonic hedgehog signaling and medulloblastoma consequent to IFN-alpha-stimulated STAT2-independent production of IFN-gamma in the brain. J Clin Invest 112:535–543. doi:10.1172/JCI18637
80. Wang X, Dubuc AM, Ramaswamy V, Mack S, Gendoo DM, Remke M, Wu X, Garzia L, Luu B, Cavalli F et al (2015) Medulloblastoma subgroups remain stable across primary and metastatic compartments. Acta Neuropathol 129:449–457. doi:10.1007/s00401-015-1389-0
81. Wefers AK, Warmuth-Metz M, Poschl J, von Bueren AO, Monoranu CM, Seelos K, Peraud A, Tonn JC, Koch A, Pietsch T et al (2014) Subgroup-specific localization of human medulloblastoma based on pre-operative MRI. Acta Neuropathol 127:931–933. doi:10.1007/s00401-014-1271-5
82. Wetmore C, Eberhart DE, Curran T (2001) Loss of p53 but not ARF accelerates medulloblastoma in mice heterozygous for patched. Cancer Res 61:513–516
83. Wu X, Northcott PA, Dubuc A, Dupuy AJ, Shih DJ, Witt H, Croul S, Bouffet E, Fults DW, Eberhart CG et al (2012) Clonal selection drives genetic divergence of metastatic medulloblastoma. Nature 482:529–533. doi:10.1038/nature10825
84. Yang ZJ, Ellis T, Markant SL, Read TA, Kessler JD, Bourboulas M, Schüller U, Machold R, Fishell G, Rowitch DH et al (2008) Medulloblastoma can be initiated by deletion of patched in lineage-restricted progenitors or stem cells. Cancer Cell 14:135–145
85. Zurawel RH, Chiappa SA, Allen C, Raffel C (1998) Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res 58:896–899