Medulloblastomas are the most common cerebellar tumors of central in childhood (1). They are neuroepithelial tumors arising from the cerebellum and account for ~20% of all intracranial tumors in children, and for 40% of all childhood posterior fossa tumors. Although medulloblastoma peaks at 8 years of age, ~30% of medulloblastomas occur in adults (2).

Medulloblastoma arises from remnants of the primitive neuroectoderm in the roof of the fourth ventricle. It grows in cerebellar vermis and fills the ventricle, often invading through the ependyma in the floor of the ventricle to enter the brainstem. Less commonly, the tumor arises in the cerebellar hemisphere (3). The histogenesis of this tumor has been controversial for many years. Some authors support the idea that it arises primarily from primitive neuroectodermal cells in the germinal matrix surrounding the ventricle. According to another study, medulloblastomas have been shown to express the \textit{ZIC1} gene, which is normally expressed only in the external granular layer of the developing cerebellum, suggesting that this tumor arises from external granular layer precursor cells (4). It is also possible that cells from both of these locations give rise to medulloblastomas. In fact, there might be more than one cell type; the nodular variant originating from the external granular layer, and the classic histotype from cells of the subventricular matrix (1, 5). Historically, medulloblastomas and other central nervous system embryonal tumors are classified on the basis of their location within the central nervous system, and of their histologic features. Five histologic variants are recognized according to the WHO: (a) the classical variant medulloblastoma, in which the cells occasionally display features of neuroblastic differentiation; (b) desmoplastic medulloblastoma, in which tumor cells commonly show neurocytic differentiation, and are surrounded by a collagen-rich extracellular matrix; (c) large-cell anaplastic medulloblastoma, associated with poor prognosis and short survival; and finally (d) the melanotic and (e) medullomyoblastoma variants, which are less common (1, 5). Clinical outcome of patients with medulloblastoma varies according to age, postoperative tumor residuum, and metastatic stage (1). Therefore, this disease is also classified according to risk-adapted treatments. High-risk patients with medulloblastoma are distinguished from standard-risk patients, because they are either 3 years old or younger, have metastases, or show residual tumor postoperation, and should receive more intensive treatment (1).

Over the past decade, new discoveries in molecular biology have shown evidence that classification of embryonal tumors by histology and clinical criteria should also include the identification of specific gene mutations which could be necessary to differentiate medulloblastoma from other highly malignant tumors, otherwise not detectable by morphologic criteria (3). This review summarizes the signaling pathway alterations identified in medulloblastoma, with a particular attention on the...
Molecular Biology of Medulloblastoma

**Genetic alterations and aberrant signaling pathways in medulloblastoma.** Medulloblastoma is a heterogeneous cancer of unknown etiology. An important contribution to the understanding of medulloblastoma came from the study of the Gorlin’s syndrome and the Turcot’s syndrome, two genetic disorders which show an unusual predisposition to medulloblastoma formation (6, 7).

Gorlin’s syndrome, or basal cell nevus syndrome, is a rare autosomal dominant disorder associated with skeletal anomalies, large body size, and a high incidence of basal cell carcinoma and medulloblastoma (3). It is characterized by germ line mutations of the *PTCH* gene, which encodes for a transmembrane protein capable of binding the Hedgehog (HH) family of signaling proteins (6, 8). How changes in *PTCH* and other pathway components predispose to medulloblastoma is currently under investigation. During the normal development of the cerebellum, *PTCH* is able to maintain the sonic hedgehog (SHH) pathway in the off state by interacting with smoothened protein (SMO). Upon binding of SHH, which is secreted by Purkinje cells, *PTCH*-mediated repression is alleviated and a signal is transduced to the nucleus to promote the proliferation of granule cells (9). Because most medulloblastomas seem to originate from this cell lineage, deletion of *PTCH* in granule-neuron precursor cells might result in malignant transformation. Mutations in the HH pathway may promote its constitutive activation and dis regulate proliferation of granule cells to induce medulloblastomas (8). Mutations or deletions of the *PTCH* locus, and of the suppressor of fused (SUFU) locus, a downstream molecule of the HH signaling cascade, have recently been associated with sporadic medulloblastomas (8). The molecular and biological analyses of medulloblastoma have identified new markers that could be potentially used for risk stratification and clinical trials. For example, the expression of several growth factor receptors has been linked to both good and poor prognosis: TrkC, the neurotrophin-3 receptor, for instance, has been found to be associated with favorable prognosis (1, 14). In fact, the biological actions of TrkC activation affect medulloblastoma outcome by inhibiting tumor growth through the promotion of apoptosis (14).

**Association with viral infections.** Several lines of evidence suggest an association between the occurrence of medulloblastoma and the human neurotropic polyomavirus JC (JCV; ref. 16). More than 80% of neonatal hamsters inoculated intracerebrally, i.p., or s.c. with strains of JCV, isolated from progressive multifocal leukoencephalopathy lesions, develop a wide range of tumors including medulloblastomas, neuroblastomas, and pineocytomas (16, 17). Although the mechanism of JCV-induced neurotumorigenesis is not entirely clear, several studies point to the involvement of the viral early protein, T antigen, in this process. One of these studies showed that transgenic mice constitutively producing T antigen under the control of JCV early promoters/enhancers develop adrenal neuroblastomas, primitive-appearing mesenteric tumors and development of new molecular targets to improve the clinical management of this disease.
The oncogenic properties of JCV T antigen result, at least in part, from its ability to bind and inactivate tumor suppressor and cell cycle regulatory proteins, such as p53 and the pRb family of proteins (pRb; ref. 17). Del Valle et al. (16) showed, by immunohistochemical analysis, a correlation between T antigen, p53, and pRb/p105 expression in medulloblastoma. In addition, a significant immunoreactivity to the pRb-related proteins, p107 and pRb2/p130, was observed in most of the T antigen–positive cases, suggesting that association between T antigen and p53 and/or pRbs occurs in these tumors. These findings provide indirect evidences that JCV, acting through T antigen, might be involved in the formation and progression of these tumors (16). Because of the low frequency of p53 mutations, most medulloblastomas (40-60%) with increased p53 expression overexpress the wild-type protein. It is also of interest that high p53 expression in medulloblastoma has been correlated with a poor prognosis. The finding of T antigen positivity and p53 overexpression suggests that JCV induction of medulloblastoma might be considered as a prognostic factor for patients with medulloblastoma (16).

Medulloblastoma and pRb family of tumor suppressor genes. The pRb family is a group of nuclear proteins including pRb/p105, p107, and pRb2/p130. These proteins are the major regulators of cell proliferation and cell differentiation through their ability to suppress cell cycle progression (17–19). Although pRb/p105 does not seem to be mutated in medulloblastomas, it has been identified as a tumor suppressor gene deleted or mutated in childhood retinoblastoma and in a variety of adult cancers (18). The role of p107 and pRb2/p130 in tumor suppression is less clear than that of pRb/p105, but there are several reports of pRb2/p130-inactivating mutations identified in human cancers (20–22). In humans, pRb/p105 mutations have been found in high-grade astrocytic tumors, and the loss of its function is considered to be involved in the progression from the benign form to the highly malignant astrocytoma. Therefore, the lack of an initiation step might be responsible for the lack of tumor formation of pRb/p105-null mutant astrocytes. Evidences suggest that loss of p53 function could be the initiator event in low-grade astrocytomas (23). Marino et al. (23) have studied the role of pRb/p105 in the neoplastic transformation of astrocytes. In their study, a mouse model for medulloblastoma was generated by Cre-LoxP–mediated inactivation of pRb and p53 in the external granular layer cells. They observed that pRb/p105 was not required for normal maturation of astrocytes, and that the independent inactivation of p53 or pRb/p105 was not sufficient to cause the neoplastic transformation of these cells “in vivo.” These authors showed that pRb/p105 somatic inactivation, in combination with a somatic or a germ line p53 inactivation, leads to medulloblastomas in mice (23). Furthermore, it was evidenced that the biologically active NH2-terminal fragment of SHH acts to up-regulate and maintain the cyclin-retinoblastoma axis by regulating the cyclins CCND1, CCND2, and CCNE mRNA transcript and protein levels in a subset of primary cultures from neonatal murine cerebellum (24). SHH-induced CCND and CCNE expression clearly associated with cell cycle progression, as hyperphosphorylation of pRb/p105 and increased levels of DNA synthesis were observed (24). Therefore, activating mutations in the HH pathway, important for medulloblastoma formation, may cause alterations in the phosphorylation status of pRb/p105.

Although there is no evidence regarding alterations of the pRb2/p130 pathway in medulloblastoma, it seems to be implicated in glioblastoma. In fact, one study shows that pRb2/p130 plays a role in radiation-induced cell death, indicating that the antitumoral activity of pRb2/p130 could regulate both the inhibition of cell cycle progression and induction of cell death (25).

Current Therapies

The standard treatment for medulloblastoma, based on clinical staging criteria, has been surgery followed by craniospinal radiotherapy, resulting in a 5-year survival rate of 50% to 60% (1). Radiation therapy, at a dose of at least 55 Gy to the tumor, has been shown to prolong survival and results in cures. Because of the tendency of the tumor to spread in the cerebrospinal fluid, an additional 35 Gy is given to the entire brain and spinal cord (1, 3). Despite whole brain and spinal radiation for prevention and dissemination, almost half of the patients die of early tumor recurrence, and most survivors suffer significant neurocognitive sequelae as a result of this therapy (1, 3). Unfortunately, this therapy causes devastating effects on the intellect; furthermore, children’s growth could be impaired as a result of growth hormone deficiency, early puberty development (mainly in girls), and compromised spinal growth (1, 3).

Medulloblastoma is also a relatively chemosensitive tumor. Single-agent drug trials have shown the activity of various drugs, including methotrexate, high-dose cyclophosphamide, and platinum derivatives such as cisplatinum and carboplatinum in children with recurrent medulloblastoma (26, 27). In particular, as a single agent, high-dose cyclophosphamide was shown to result in objective tumor shrinkage whereas cisplatinum resulted in objective tumor response in nearly 75% of patients (28, 29). More recently, combination chemotherapy such as 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, vincristine, and cisplatinum has been used with positive results in children with recurrent medulloblastoma (28). Another study has shown a relatively high response rate with the combination of ifosfamide, carboplatinum, and etoposide (26, 30). Although chemotherapy could result in long-term disease control in a subset of infants and young children with medulloblastoma, most patients will not be cured after receiving chemotherapy treatment alone. Neither has the use of a high-dose chemotherapy regimen shown increased long-term disease control rate (31). The late toxicities of therapy are also equally important, and current approaches to this tumor treatment involve a balance between maximizing cures whereas limiting long-term sequelae of treatment. Another problem is the blood-brain barrier, which restricts the entry of hydrophilic and large lipophilic compounds into the brain (32). Trials have shown that craniospinal radiotherapy and reduced-dose or hyperfractionated craniospinal radiotherapy, together with chemotherapy, can improve overall survival and reduce the risk of radiotherapy-related cognitive and endocrine effects (33, 34). For instance, chemotherapy, including DNA alkylating agents such as athylnitrosoureas and platinum derivatives (which have shown efficacy against medulloblastoma) have been used in association with radiation therapy in older patients, especially...
in those with cerebrospinal fluid metastases at presentation (3). Several chemotherapeutic regimens have been investigated for the treatment of medulloblastoma, as shown in Table 1. Verlooy et al. (35) have analyzed preradiotherapy chemotherapy in high-risk patients in order to treat microscopic metastasis and to reduce the tumor burden prior to radiotherapy. In general, these studies have shown that the combination of postradiotherapy chemotherapy and surgery is more effective than radiation and surgery (26). It was also investigated if intensive postoperative chemotherapy alone could improve survival and cognitive function in young children. This treatment is based on three cycles of intravenous chemotherapy and intraventricular methotrexate instead of radiotherapy, and has been shown to be a promising treatment in young children without metastases (36).

The combination of chemotherapy and radiotherapy has currently improved the 5-year survival rate to 55% to 76% for high-risk patients and 70% to 80% for standard-risk patients (1).

Despite these improvements in overall survival rate after the multimodality treatment including surgery, radiation, and chemotherapy, a small but substantial number of patients will have recurrent or progressive disease. Unfortunately, attempts to further reduce the morbidity and mortality associated with medulloblastoma have been restricted by the toxicity of conventional treatments and the infiltrative nature of the disease (1).

### Conclusions and Future Perspectives of Molecular Biology to Therapy

Currently, many strides have been conducted in the field of medulloblastoma, and several molecular modifications have been identified, the elucidation of which might have direct effects on tumor management (1, 3). In fact, a better understanding of the genetic events underlying the pathology of these tumors may contribute to the development of new more effective and less harmful clinical strategies. Many lines of evidences suggest that response to the treatment is not determined by chance, but rather by the biology of the tumor (1, 3). Furthermore, drugs that target cell signaling pathways implicated in the formation of medulloblastomas might provide an alternative to conventional cytotoxic approaches of cancer treatment, decreasing treatment-related toxicity (1, 3).

In one study, gene expression profiling was able to distinguish classic and desmoplastic medulloblastomas and to separate a series of medulloblastomas from malignant gliomas and atypical teratoid/rhabdoid tumor (1, 3). Atypical teratoid/rhabdoid tumor was delineated as an embryonal tumor with poor prognosis and linked with mutations of the INI1/SNF5 gene (1, 3). They cannot be distinguished from medulloblastomas by histologic criteria alone; thus, mutation analysis of INI1/SNF5 is essential to establish diagnosis (1, 3).

Combining molecular and histopathologic analyses of tumors, together with clinical staging, might identify patients who can be cured with very low-intensity treatment, patients requiring moderate therapy, or patients who require very intensive or experimental treatment. For instance, a multicenter study showed that combining tumor ERBB2 expression and analysis of the clinical features of the patient permits a better assessment of the disease risk than clinical factors alone, even if this study needs to be confirmed in large prospective clinical trials (37, 38).

In this study, all of the children with standard-risk ERBB2-negative disease were alive at 5 years, compared with only 54% for children with standard-risk ERBB2-positive cancer. Numerous growth factor receptors have been considered molecular markers, and may be used for the stratification of tumor in clinical trials, such as TrkC, which has been associated with good prognosis, and ERBB2, platelet-derived growth factor receptor-α, insulin-like growth factor receptor 1 which have been associated with poor prognosis (14, 39).

In a variety of childhood malignancies, a risk-adapted therapy, according to both disease status and molecular profile,

### Table 1. Summary of data obtained in clinical trials in medulloblastoma

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Trial and accrual period</th>
<th>Treatment (Gy, posterior fossa/craniospinal axis)</th>
<th>5-y survival rate (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(26) HIT’91, 1991-1997</td>
<td>Preradiation (55.2/35.2) ifosfamide, methotrexate, etoposide, cytarabine vs. postradiation (55.2/35.2) lomustine, vincristine and cisplatin</td>
<td>65 vs. 78</td>
<td>&lt;0.03</td>
<td></td>
</tr>
<tr>
<td>(30) SIOP III, 1992-2000</td>
<td>Preradiation (55/35) cyclophosphamide, vincristine, etoposide and carboplatin vs. radiation (55/35)</td>
<td>74 vs. 60</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>(48) CCG9892, 1990-1994</td>
<td>Postradiation (55.2/23.4) vincristine, lomustine, and cisplatin</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(27) SJMB’96, 1996-1999</td>
<td>Postradiation (55/23.4) high-dose cyclophosphamide, cisplatin and vincristin</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(49) POG8631/CCG923, 1986-1990</td>
<td>Radiation (54/36) vs. radiation (54/23.4)</td>
<td>67 vs. 52</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(50) CCG921, 1986-1992</td>
<td>Postradiation (54/36) vincristine, lomustine and prednisolone vs. eight drugs in 1 d preradiation and postradiation (54/36)</td>
<td>63 vs. 43</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>(27) SJMB’96, 1996-1999</td>
<td>Preradiation topotecan window then high-dose cyclophosphamide, cisplatin, and vincristin</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(29) Limited institution CHOP/CNMC/CMCD, 1983-1993</td>
<td>Postradiation (55.2/36) postradiation (55.2/36) vincristin, lomustin, and cisplatin</td>
<td>67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Molecular Biology to Therapy in Medulloblastoma

is currently considered routine. Thus, accurate disease risk assessment for patients with medulloblastoma might also be possible considering clinical and molecular prognostic markers (1, 3). At present, clinical trials of medulloblastoma by the Children’s Oncology Group are associated with biological studies aimed at validating molecular markers as outcome predictors, which will be used for risk stratification (1, 3).

Currently, numerous anticancer drugs are designed to target a specific protein or a signaling pathway. The efficacy of several of these molecules is now being investigated in medulloblastomas. Among these, cycloamine is a plant-derived teratogen, the inhibitory activity of which acts on the SHH pathway by binding to, and inactivating, smoothened protein (SMO; ref. 40). Cycloamine seems to interfere with this pathway by modulating the SMO function (41). In particular, this inhibitory effect is mediated by a direct binding of cycloamine to the heptahelical bundle of SMO, likely affecting the protein conformation. This drug is able to target the SHH pathway, inhibiting SHH-dependent gene expression in medulloblastoma in vitro, and is able to cause cell cycle arrest consistent with the initiation of neuronal differentiation and loss of neuronal stem cell–like character (41, 42). This compound also causes the regression of murine tumor allografts in vivo and induces rapid death of cells from freshly resected human medulloblastomas, but not from other brain tumors (41, 42). Other inhibitors of the SHH pathway, such as IhHAnTag, are in preclinical studies (43).

Medulloblastoma is a highly invasive tumor, which is generally disseminated at the time of diagnosis. Furthermore, conventional therapeutic approaches have not reduced the mortality associated with metastatic medulloblastoma (1, 3, 8, 28). Thus, it is very important to find agents that are able to reduce tumor invasiveness. In fact, another class of potential molecular-targeted therapies for medulloblastoma is represented by small molecule inhibitors of receptor tyrosine kinases. These include dual-specific inhibitors of ERBB1 or ERBB2 activity, such as OSI-774 (erlotinib; ref. 44). This drug is able to inhibit ERBB2 signaling in medulloblastoma in vitro and in vivo. Treatment with this drug selectively blocks ERBB2-dependent prometastatic gene up-regulation and reduces the invasiveness of medulloblastoma cells (44). At present, the inhibitors of ERBB1 or ERBB2 activity are in phase I and phase II clinical trials in children with brain tumors in the Children’s Oncology Group and the U.S. Pediatric Brain Tumor Consortium (44).

Inhibitors of the SHH and ERBB2 pathways represent a great promise as a first-generation molecular-targeted therapy for medulloblastoma, even if the development of these agents for routine clinical use will not be easy (43, 44).

It is very important to develop agents that are able to block Wnt signaling, given its activation in medulloblastoma (12, 45). Lawinger et al. (12) have shown that neural silencer element NRSF/REST, which is transcriptionally regulated by the Wnt cascade, is highly expressed in medulloblastoma cell lines and that cell growth is inhibited by specific molecular blocking agents. Dkk-3 and FRPs are Wnt signaling antagonists that could be used as natural inhibitors of this pathway in cancer therapy. In fact, expression of Dkk-3 is down-regulated in human immortalized and tumor-derived cell lines and the expression of the exogenous Dkk-3 gene in small cell lung cancer caused the inhibition of cell proliferation (45). Furthermore, it was shown that transient expression of a recombinant transcription factor, REST/VP16, was able to compete with the endogenous REST/NRSF for DNA binding (12). It counteracts the NRSF/REST-mediated inhibition of neuronal promoters, causing stimulation of endogenous neuronal gene expression and induction of apoptosis. There are other inhibitors of this pathway, but they are still in preclinical studies and, hopefully, should reach clinical trials in the next few years (12).

Line-1 (L1) are abundant retrotransposons that comprise ~20% of mammalian genome (46). In particular, they are endowed with a reverse transcriptase–coding gene which enables them to retrotranspose autonomously (46). Engineered human L1 harboring a retrotransposition indicator cassette could retrotranspose in adult rat neural progenitor cells in vitro and in the brains of transgenic mice in vivo. It has been shown that these events could influence both neuronal gene expression and differentiation in neural progenitor cells in vitro (46). According to the study by Sciamanna et al. (47), two characterized reverse transcriptase inhibitors, nevirapine and efavirenz, seem to reduce proliferation, induce morphologic differentiation, and reprogram gene expression in melanoma and prostate cancer cells. Thus, the use of reverse transcriptase inhibitors might represent a novel approach to block cell growth and to induce differentiation in medulloblastoma, and in addition, might overcome the problem of the blood-brain barrier because most of these inhibitors are lipophilic.4

Elucidation of crosstalk of the pathways during tumor formation is required in order to study how these anticancer drugs could be combined. Moreover, a deeper understanding of the molecular mechanisms of the resistance to cytotoxic chemotherapy and radiotherapy might allow the combination of molecular and conventional therapies in the very near future.

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