ERBB2 in Pediatric Cancer: Innocent Until Proven Guilty

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Review the key aspects of ERBB2 signal biology in normal and cancer cells.
2. Outline available evidence for the involvement of ERBB2 signaling in different pediatric solid cancers.
3. Describe the key challenges associated with translating molecular targeted therapies of adult cancers to pediatric patients.

ABSTRACT
Adult oncologists and their research colleagues have “led the charge” in the war on cancer. Their efforts have generated effective new chemotherapies that target cancer causing molecular alterations. It is hoped that these successes will be repeated within the pediatric oncology community. Testing whether molecular targeted therapies of adult cancers are also effective against childhood cancers might allow the rapid introduction of these exciting new agents into the pediatric clinic. However, it is imperative that we do not introduce blindly these agents into the pediatric population. We must ensure that molecular targets in adult cancers also fulfill a number of important criteria within the pediatric disease. This review addresses the issues surrounding the identification of molecular targets in pediatric cancers by focusing on studies of the ERBB2 oncogene. The Oncologist 2005;10:508-517

INTRODUCTION
The identification of cancer-causing gene mutations [1, 2] has presented researchers with completely new targets for drug development [3–5]. In contrast to conventional chemotherapeutic drugs that nonspecifically target both cancerous and normal cells and thereby induce many side effects, new drugs that specifically target mutant cancer proteins hold great promise for achieving cure with minimal toxicity [6–9].

So far, only a handful of molecularly targeted therapies has been approved for clinical use. However, the recent mapping of the human genome [10], the development of genome-wide profiling techniques [11–15], and advances in chemical and structural biology have dramatically accelerated the development of molecularly targeted therapies of human cancers. This progress has fostered a sense of expectancy among the medical and lay communities that new treatments of all cancers
are “just around the corner.” However, while the number of candidate targeted therapies of adult cancers will increase over the next several years, it is unclear if similar progress will be made in pediatric cancers. Relative to the adult disease, very little is known regarding the molecular alterations that cause childhood cancers. Cooperative efforts are under way to conduct large-scale genome-wide mapping of genetic alterations in pediatric tumors; however, even if exciting new targets are discovered within subgroups of pediatric cancers, it is not clear if pharmaceutical companies will be willing to develop drugs for such a small market.

The lack of candidate molecular drug targets of pediatric cancers has led a number of research groups to adopt an alternative strategy for developing new treatments of childhood cancer. In short, this approach seeks to assess whether validated molecular treatment targets of adult cancers might also be used in the management of pediatric cancers. At first glance, this approach seems to have clear advantages. First, one might predict considerable overlap in the fundamental cell signaling pathways that are disrupted during the development of most adult and pediatric cancers [1]. Second, many of the molecular alterations observed in adult cancers have been subject to extensive preclinical and clinical study, providing a wealth of information regarding the basic biology and clinical role of these alterations in malignant disease. Third, key molecular alterations in adult cancers often have a large number of corresponding pharmacologic inhibitors that could be channeled into appropriate pediatric studies.

While efforts in adult cancer research have yielded a “shelf-full” of potential new anticancer drugs, it is imperative that we do not blindly introduce these agents into the pediatric population. We must ensure that molecular targets in adult cancers also fulfill a number of important criteria within the pediatric disease. A valid molecular drug target should not only be expressed and functioning within cancer cells, but it should also play a positive role in maintaining the malignant phenotype. Confirming these characteristics is not easy and will require concerted collaboration between the pediatric medical and research communities.

ERBB2 represents one of the first validated therapeutic targets of an adult cancer—breast cancer—to be studied as a potential drug target in pediatric malignancies. Efforts to translate this target from the adult to the pediatric oncology arena are proving controversial and complex; however, they can also teach us important lessons that should help increase the efficient development of new drugs for children with cancer.

### A Brief Review of ERBB2 and Its Role in Adult Cancer

**Neu**, the rodent orthologue of human ERBB2, was first identified as an oncogene in chemically induced rat brain tumors [16, 17]. Subsequent analysis of human tissues identified amplification of ERBB2 in some salivary carcinomas [18] and poor-prognosis breast cancers [19, 20]. These early reports stimulated huge interest in the role of ERBB2 in human cancer that has resulted in the publication of numerous studies on the biology and clinical significance of ERBB receptor signaling. These data have been comprehensively reviewed elsewhere [21–29]. Therefore, only a brief summary of the biology of ERBB2 signaling and its role in adult cancers is provided here.

The receptor tyrosine kinase (RTK) I family, which includes the epidermal growth factor receptor (EGFR), ERBB2, ERBB3, and ERBB4, interacts through a complex signaling network of ligand-mediated transmembrane homo- and heterodimers [23, 25, 30–35]. In contrast to the other family members, ERBB2 is not a primary receptor for any ligand. Rather, under physiological conditions, it is activated following heterodimerization with other RTK I receptors [32]. Recent crystallographic studies have identified significant structural differences between ERBB2 and the three other RTK I receptors that may explain the lack of a direct ligand of ERBB2 [36]. These data show that ERBB2 exists in a constitutively active state in which the region of the receptor that mediates dimerization—the “dimerization arm”—is permanently exposed (Fig. 1). In contrast, the other RTK I receptors must undergo a dramatic structural rearrangement following ligand binding for the

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**Figure 1.** ERBB receptor dimerization. Binding of ligand (L) to ERBB3 monomers unmasks the dimerization arm. ERBB2 monomers are constitutively extended and are able to dimerize with ERBB3, resulting in receptor phosphorylation (P) and cell signaling. Active ERBB2/ERBB3 heterodimers generate potent proliferative cell signals via a variety of pathways, including the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways.
dimerization arm to be unmasked (Fig. 1). Dimerization of ERBB receptors leads to phosphorylation of receptor C-terminal tyrosine residues. Once phosphorylated, these tyrosines serve as Src homology (SH)2 domain docking sites for adapter and enzyme molecules that trigger signaling cascades, including the mitogen-activated protein kinase (MAPK) [30], phosphatidylinositol 3-kinase (PI3K)/Akt [37], and signal transducer and activator of transcription (STAT) [38] pathways. This tightly regulated network controls critical cell functions involved in proliferation [25, 30], apoptosis [39], migration [40], survival [41, 42], and differentiation [43]. The role of ERBB receptor signaling in normal cell biology has been extensively reviewed elsewhere [23, 44] and is not detailed further here.

Breakdown of normal ERBB2 signaling control has catastrophic effects on cell biology [45–50]. ERBB2 overexpression disrupts the RTK I network by forcing the formation of abnormal ERBB2 homodimers and by increasing signaling through potent ERBB2-inclusive heterodimers [48, 50–53]. The ability of ERBB2 to form spontaneous homodimers when expressed at high levels probably occurs as a result of its unique constitutively exposed dimerization arm [36]. A number of model systems have demonstrated the potent transforming capacity of ERBB2 [25, 53–59]. These include transgenic models of breast cancer driven by overexpression of Neu under the control of the mammary tumor virus long terminal repeat [54].

The great majority of studies of ERBB2 in human tumor material has focused on breast cancer, resulting in the publication of data from more than 27,000 tumors [28, 29]. These studies demonstrate that ERBB2 is amplified and/or overexpressed in approximately 20% of breast cancers, and that the presence of this molecular alteration is associated with a significantly worse clinical outcome. Breast cancer has also provided the major focus for the development of anti-ERBB2 therapeutics. Of particular note, the anti-ERBB2 monoclonal antibody trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com), which has shown significant therapeutic benefit among women with ERBB2-expressing metastatic breast cancer [9, 60, 61], is now approved for the treatment of this patient population.

**DOES ERBB2 SIGNALING PLAY A SIGNIFICANT PART IN THE BIOLOGY OF PEDIATRIC CANCERS?**

ERBB2 expression has been studied in more than 800 pediatric solid tumors, including samples of medulloblastoma [62–65], ependymoma [66], osteosarcoma [67–75], Ewing’s tumor [73, 76], and Wilms’ tumor [77, 78] (Table 1). While these studies demonstrate that a significant number of pediatric solid tumors contain detectable ERBB2 RNA and protein, the pattern of ERBB2 expression observed in these tumors is very different from that seen in adult carcinomas. Cancers of the adult breast, gastrointestinal tract, and ovary frequently amplify ERBB2 and display high levels of cell membrane–associated ERBB2 protein when analyzed by immunohistochemistry (Fig. 2) [79–83]. In contrast, pediatric cancers rarely amplify ERBB2 (Table 1) and generally express relatively modest levels of ERBB2 protein that yield a more diffuse cytoplasmic immunohistochemical pattern (Fig. 2).

The finding that pediatric cancers do not recapitulate the pattern of ERBB2 expression seen in adult carcinomas has led some investigators to question the role of ERBB2 in the biology and therapy of pediatric tumors [70, 84]. However, it is now clear that gene amplification and intense membrane–associated expression are not the only mechanisms by which ERBB2 signaling is activated in human cancer. For example, less than 2% of samples of non-small cell lung cancer (NSCLC) amplify ERBB2 or display the pattern of intense ERBB2 membrane immunoreactivity that is observed in breast cancer [85]. However, up to one fifth of ERBB2-expressing NSCLCs, particularly adenocarcinomas, contain activating mutations in the kinase domain of ERBB2 [86, 87]. These mutations are not associated with high-level ERBB2 expression [86], but they are remarkably similar to mutations found in the kinase domain of EGFR that predict the sensitivity of NSCLC to gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com), an inhibitor of the EGFR kinase [8, 88]. Mechanisms that can lead to aberrant expression of ERBB2 in the absence of gene amplification have also been described, including an increased rate of gene transcription [89, 90]. Thus, it is inappropriate to approach the analysis of pediatric cancers with the assumption that amplification and/or overexpression of ERBB2 are the sole indicators of aberrant receptor signaling. However, it is equally inappropriate to conclude that any expression of ERBB2 is pathogenic. Rather, to determine the biologic and clinical significance of ERBB2 in pediatric cancers, it is important to address a number of fundamental questions: (a) Is ERBB2 expressed in the cancer of interest? (b) How does this expression relate to the normal pattern of RTK I expression in the tissue of origin of the cancer? (c) To what extent does ERBB2 engage cell signaling pathways in the cancer cell and is there evidence of aberrant receptor activation (e.g., kinase domain mutations)? (d) Does ERBB2 expression correlate with markers of aggressive disease?
Brain Tumors
Medulloblastoma, a malignant tumor of the cerebellum, was one of the first childhood cancers in which ERBB2 expression was demonstrated [91]. Subsequent immuno-
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Table 1. ERBB2 expression, amplification, and prognostic significance in pediatric cancers

<table>
<thead>
<tr>
<th>Disease</th>
<th>ERBB2 expression</th>
<th>ERBB2 amplification</th>
<th>Survival significance</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method (Ab)</td>
<td>% Positive(^a) (n)</td>
<td>Method (% Amplified (n))</td>
<td>(p value)</td>
</tr>
<tr>
<td>MB/PNET</td>
<td>IHC (CB11)</td>
<td>41 (29) qPCR 0 (0/31)</td>
<td>Decreased (&lt;.004)</td>
<td>Gilbertson et al. [63]</td>
</tr>
<tr>
<td>45</td>
<td>IHC (CB11)</td>
<td>13 (6) — —</td>
<td>Decreased (&lt;.005)</td>
<td>Herms et al. [64]</td>
</tr>
<tr>
<td>81</td>
<td>WB (CB11)</td>
<td>40 (32) — — 51 (32)</td>
<td>Decreased (&lt;.05)</td>
<td>Gajjar et al. [62]</td>
</tr>
<tr>
<td>119</td>
<td>IHC (CB11)</td>
<td>16 (19) — —</td>
<td>Decreased (&lt;.005)</td>
<td>Ray et al. [65]</td>
</tr>
<tr>
<td>EP</td>
<td>IHC (CB11)</td>
<td>78 (46) SB 0 (0/10)</td>
<td>Decreased(^b) (&lt;.0001)</td>
<td>Gilbertson et al. [66]</td>
</tr>
<tr>
<td>59</td>
<td>WB (CB11)</td>
<td>95 (19) SB 0 (0/10)</td>
<td>Decreased (&lt;.01)</td>
<td>Onda et al. [68]</td>
</tr>
<tr>
<td>26</td>
<td>WB</td>
<td>42 (11) SB 0 (0/26)</td>
<td>Decreased (&lt;.05)</td>
<td>Gorlick et al. [67]</td>
</tr>
<tr>
<td>47</td>
<td>IHC</td>
<td>43 (20) SB 0 (0/26)</td>
<td>Decreased (&lt;.05)</td>
<td>Akatsuka et al. [74]</td>
</tr>
<tr>
<td>81</td>
<td>IHC</td>
<td>51 (61) SB 0 (0/26)</td>
<td>Normal (&lt;.05)</td>
<td>Maitra et al. [75]</td>
</tr>
<tr>
<td>21</td>
<td>IHC (A0485)</td>
<td>0 (0) FISH 0 (0/21)</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>66</td>
<td>IHC (A0485)</td>
<td>31 (47) FISH 0 (0/21)</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>36</td>
<td>RT-PCR</td>
<td>0 (0) — —</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>25</td>
<td>IHC (Ab-3)</td>
<td>44 (25) FISH 66 (8/21)</td>
<td>Decreased (&lt;.04)</td>
<td>Zhou et al. [72]</td>
</tr>
<tr>
<td>27</td>
<td>IHC (A0485)</td>
<td>11 (3) FISH 0 (0/1)</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>19</td>
<td>IHC (A0485)</td>
<td>31 (6) FISH 0 (0/1)</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>Ewing's</td>
<td>IHC (A0485)</td>
<td>27 (3) — —</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>11</td>
<td>IHC (A0485)</td>
<td>27 (3) — —</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>12</td>
<td>RT-PCR</td>
<td>0 (0) — —</td>
<td>None (NS)</td>
<td>Thomas et al. [73]</td>
</tr>
<tr>
<td>13</td>
<td>IHC (A0485)</td>
<td>0 (0) FISH 0 (0/13)</td>
<td>None (NS)</td>
<td>Ye et al. [76]</td>
</tr>
<tr>
<td>Wilms'</td>
<td>IHC (3B5)</td>
<td>34 (21) — —</td>
<td>None (NS)</td>
<td>Ghanem et al. [78]</td>
</tr>
<tr>
<td>62</td>
<td>IHC (CB11)</td>
<td>93 (13) — —</td>
<td>None (NS)</td>
<td>Pinthus et al. [77]</td>
</tr>
</tbody>
</table>

\(^a\)ERBB2 immunopositivity was defined differently in each of these studies.

\(^b\)Significance when combined with other molecular prognostic markers.

Abbreviations: Ab, antibody; EP, ependymoma; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MB/PNET, medulloblastoma/primitive neuroectodermal tumor; NS, not significant; OS, osteosarcoma; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse-transcription–polymerase chain reaction; SB, Southern blotting; WB, Western blotting.
reaction (RT-PCR) analyses have also identified ERBB2 mRNA in almost all medulloblastomas [92, 93]. In addition to ERBB2, medulloblastomas frequently express the three other RTK I family members. This is particularly true of ERBB4, which has been identified in association with ERBB2 and often incorporated into ERBB2/ERBB4 heterodimers, in over half of all primary tumors [63].

Studies of ERBB2 expression in medulloblastoma have also demonstrated a consistent association between expression of this receptor and poor patient prognosis (Table 1). In an immunohistochemical analysis of 70 medulloblastomas, Gilbertson et al. [63] reported a worse prognosis among patients whose tumors exhibited high ERBB2 expression (≥50% immunopositive tumor cells, \( p < .004 \)). Further, coexpression of ERBB2 and ERBB4 was independently associated with a lower overall survival (\( p < .0001 \)), suggesting ERBB2 may promote an aggressive medulloblastoma phenotype through synergistic interaction with ERBB4. Tumors with high ERBB2 expression also demonstrated a significantly greater mitotic index and S-phase fraction [94] and a more advanced metastatic stage [93]. A recent immunohistochemical study by Ray et al. has confirmed these data, demonstrating a significantly worse clinical outcome for 19 of 119 children with medulloblastomas whose tumors expressed ERBB2 (\( p < .05 \)) [65]. ERBB2-expressing tumors in that study were also more likely to present with metastasis, and the survival significance of ERBB2 in that study was not independent of metastatic stage [65]. ERBB2 protein expression detected by Western blotting also predicts a worse clinical outcome among children with medulloblastomas. Gajjar et al. detected ERBB2 expression by Western blot analysis in 40% (\( n = 32/81 \)) of medulloblastomas [62]; this expression was independently associated with a poor prognosis (\( p = .031 \)). Of particular note, the combination of clinical characteristics and ERBB2 expression in that study provided a highly accurate means of discriminating disease risk. One hundred percent (\( n = 26 \)) of children in that study who had clinical average-risk, ERBB2-negative disease were alive at 5 years, with a median follow-up of 5.6 years, compared with only 54% of children with average-risk, ERBB2-positive tumors (\( n = 13; p = .0001 \)).

In contrast to the frequent expression of ERBB2 in medulloblastoma, this receptor is undetectable in the normal cerebellum during development [95]. However, evidence indicates that normal cerebellar development is dependent upon intact RTK I signaling, particularly through ERBB3 and ERBB4. Targeted disruption of these receptors results in a variety of central nervous system defects, including abnormalities of the cerebellum [96–98]. ERBB4 is expressed at high levels in granule neuron precursor cells (GNPCs) of the murine cerebellar external germinal layer (EGL) and in the internal granule cell layer during embryonic and early postnatal life. This expression falls dramatically with development, becoming undetectable by 1 month of age. In contrast, ERBB3 is absent from the cerebellum during early to mid-gestation but becomes prominent in the adult cerebellum. EGFR is expressed in a number of areas of the developing and mature cerebellum, including the subEGL and white matter regions [99]. In stark contrast, ERBB2 is undetectable in the human [93] and expressed at very low levels in the mouse cerebellum.

![Figure 2. ERBB2 protein-expression pattern in breast cancer and pediatric medulloblastoma. Immunohistochemical analysis of ERBB2 demonstrates the typical intense membrane expression pattern displayed by a breast cancer harboring amplification of ERBB2 (A). This is contrasted with the more diffuse cytoplasmic ERBB2 immunoreactivity seen in pediatric medulloblastomas expressing low (B), intermediate (C), and high (D) levels of ERBB2. (E): Western blot analysis of immunohistochemical ERBB2-positive (1) and ERBB2-negative (2) medulloblastoma samples confirm that the receptor is expressed and actively signaling (as measured by the presence of phosphorylated pERBB2\(^{Y1248}\) in this disease.](http://theoncologist.alphamedpress.org/Downloaded from http://theoncologist.alphamedpress.org)
[97] throughout development. Together, these data indicate that EGFR, ERBB3, and ERBB4, but not ERBB2, participate in normal cerebellar development and function. Thus, aberrant expression of ERBB2 in GNPCs might initiate formation of highly transforming ERBB2/ERBB4 heterodimer signaling that could contribute to the development of medulloblastoma.

Functional analyses of ERBB2 signaling in tumor cell lines have also implicated aberrant ERBB2 signaling in medulloblastoma pathogenesis. These studies demonstrate that aberrant, high-level expression of ERBB2 in medulloblastoma cells promotes receptor homodimerization [100], activates extracellular signal-regulated kinase (ERK)1/2 and Akt signals [92, 100], and upregulates prometastastic gene expression in vitro and in vivo [92].

Taken together, the results of studies of medulloblastoma appear to support a role for ERBB2 in predicting poor clinical outcome among children with this disease. Further, in vitro and in vivo data of ERBB2 signaling in medulloblastoma are now emerging that may explain the mechanism by which this signal system supports aggressive disease behavior. While these data are encouraging, the prognostic power of ERBB2 must be validated among a larger prospectively treated group of medulloblastoma patients before this marker can be used as a stratification tool for assigning therapy. Additionally, ERBB2 does not appear to be amplified in medulloblastoma, and the mechanism that leads to misexpression of ERBB2 in GNPCs remains to be determined. In this regard, there is some evidence that the AP2 transcription factor, which has been implicated in the positive regulation of ERBB2 promoter activity [89, 90], might promote ERBB2 expression in medulloblastomas [63]; however, these data remain to be confirmed. Efforts to answer these questions are now under way within prospective clinical trials of medulloblastoma that are being conducted by the Children’s Oncology Group, the International Society of Pediatric Oncology, and St. Jude Children’s Research Hospital. Furthermore, we are in the process of generating mouse models of dysregulated ERBB2 signaling during cerebellar development; these approaches should provide a better understanding of the role played by ERBB2 in medulloblastoma development.

The expression frequency and clinical significance of the RTK I family has also been reported in a single study of ependymoma [66]. This comprehensive study used immunohistochemistry, Western blotting, and RT-PCR analyses to study more than 120 samples of ependymoma. Coexpression of ERBB2 and ERBB4 was identified in over 75% of the ependymomas studied and was significantly related to tumor proliferative activity (p < .05, Ki-67 labeling index [LI]). Furthermore, combined survival analysis of clinical (degree of surgical resection) and molecular (ERBB2/ERBB4 expression status and Ki-67 LI) factors enabled a greater resolution of patient prognosis than any individual variable alone. Through analysis of short-term primary cultures of ependymomas, the authors were also able to show that ligand-dependent activation of ERBB receptor signaling resulted in Akt phosphorylation and cellular proliferation that was significantly blocked in a dosage-dependent manner using WAY-177820, a novel inhibitor of ERBB2 tyrosine kinase activity. While these data suggest that the ERBB receptor is associated with aggressive disease behavior in ependymoma, no other groups have studied RTK I expression in ependymoma, and these data await independent verification.

Osteosarcoma

The results of studies of ERBB2 expression in pediatric osteosarcoma have proved especially controversial [84]. This controversy has arisen for two reasons. First, most authors have approached the study of ERBB2 in osteosarcoma with the misconception that aberrant ERBB2 signaling in cancer cells results solely from intense membrane-associated expression [70, 101]. Second, published studies of ERBB2 in osteosarcoma have not been sufficiently powered to determine survival significance.

An unbiased view of the literature indicates that ERBB2 expression in osteosarcoma is reported with remarkable consistency. Immunohistochemical analyses involving more than 300 osteosarcomas demonstrate that cytoplasmic ERBB2 immunoreactivity occurs in approximately 40% of tumor samples (Table 1). Furthermore, real-time RT-PCR, Western blot, and flow cytometry studies of primary tumor samples and low-passage primary osteosarcoma cells have clearly demonstrated expression of ERBB2, EGFR, and ERBB4 in this disease [68, 70, 102].

While it is clear that ERBB2 is expressed in osteosarcoma, it remains to be determined whether this expression predicts prognosis or plays an active role in the disease process. Studies of the prognostic significance of ERBB2 in osteosarcoma have yielded conflicting results (Table 1). Although these discrepancies may result in part from the different techniques and reagents that have been used to study ERBB2 in osteosarcoma [70, 84], these studies have not been sufficiently powered to adequately address the survival significance of ERBB2 in osteosarcoma. Furthermore, it is not clear if ERBB2 signaling is dysregulated in osteosarcoma relative to that in normal developing bone, and there are no published studies describing the impact of ERBB2 signaling on osteosarcoma cell biology.
ERBB2 in Pediatric Cancer: Innocent Until Proven Guilty

ERBB2 expression has been convincingly demonstrated in a number of pediatric cancers. Emerging evidence suggests that tumor cell expression of ERBB2 might identify aggressive forms of medulloblastoma, and there are some data to indicate that ERBB2 signaling may promote metastasis of this disease. Consequently, a phase I/II trial of the EGFR and ERBB2 dual kinase inhibitor lapatinib (Glaxo SmithKline, Philadelphia, http://www.gsk.com) is currently under way among children with medulloblastoma within the Pediatric Brain Tumor Consortium (trial PBTC016). It is hoped that ongoing studies of ERBB2 expression in prospective clinical trials of medulloblastoma, and efforts to develop new ERBB2-based disease models, will better define the role of ERBB2 in this disease.

Although ERBB2 expression is also a feature of osteosarcoma and other solid pediatric tumors, there is no convincing evidence to suggest that ERBB2 expression predicts clinical outcome in these diseases, and functional studies of ERBB2 in these childhood cancers are lacking. Greater effort needs to be invested to provide clinical and functional evidence that ERBB2 signaling is pathogenic in these pediatric cancers before patients are committed to clinical trials of ERBB2 inhibitors.

Future Identification of Molecular Drug Targets and Prognostic Markers of Pediatric Cancer

The earliest studies of ERBB2 expression in pediatric cancers were published around 10 years ago [68, 91]. Since that time, dramatic progress has been made in the development of techniques that allow the analysis of the structure and expression of the entire genome. As a consequence, we now have access to extremely powerful tools that are enabling the identification of causative molecular alterations in human cancer. These techniques include array comparative genomic hybridization [12, 13] and high-density single nucleotide polymorphism oligonucleotide arrays [103] that can pinpoint genomic gains and losses in cancers at the level of individual genes and array-based systems that can determine genome-wide expression patterns [104]. The cost-effectiveness of these methodologies, both in terms of financial and tissue costs, has also improved dramatically over the last few years. Consequently, it is now possible to map the copy number, allelic status, and expression of thousands of genes in a single tumor sample, using the same amount of fresh tissue that was previously used to perform individual gene studies.

It seems clear that future efforts to define molecular drug targets and prognostic markers of pediatric cancers should not focus on individual gene products, but rather exploit the full power of new genome-wide technologies in the prospective analysis of tumor samples. This approach would provide understanding of the clinical significance of individual genes, such as ERBB2, identify hitherto unknown cancer genes, and provide crucial information regarding cooperating molecular alterations in childhood cancers. The identification of molecular events that are synergistic during tumor formation may be especially helpful in planning combination trials of molecularly targeted therapies. The conduct of genome-wide studies within the context of large prospective pediatric cancer clinical trials will require significant collaboration between medical and scientific personnel. Although this will not be achieved easily, this is the most efficient mechanism by which valid molecular targets will be identified for the treatment of children with cancer.

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Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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