Title

HER2/neu:An Increasingly Important Therapeutic Target: Part 2 Distribution of HER2/neu Overexpression and Gene Amplification by Organ, Tumor Site and Histology.

Author

Nelson, EL

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CLINICAL INVESTIGATION

HER2/neu: an increasingly important therapeutic target. Part 2: Distribution of HER2/neu overexpression and gene amplification by organ, tumor site and histology

Edward L Nelson
University of California, Irvine, School of Medicine; Division of Hematology/Oncology; Department of Medicine; Department of Molecular Biology & Biochemistry; Sprague Hall, Irvine, CA 92697, USA
enelson@uci.edu

No biological molecule in the field of oncology has been more extensively or more successfully targeted for therapeutic intent than the product of the *c-erbB2* gene, HER2/neu. This is the second of a comprehensive three-part review of the foundation for and therapeutic targeting of HER2/neu. The distribution of HER2/neu overexpression and/or gene amplification by individual tumor sites and histologies will be comprehensively surveyed and described. This provides a bridge between the primarily basic science focused Part I, and the survey of clinical applications to follow in Part III. In combination, this comprehensive survey will identify opportunities and promising areas for future evaluation of HER2/neu-targeted therapies, highlighting the importance of HER2/neu as an increasingly important therapeutic target.

Keywords: c-erbB2 • carcinoma • EGFR family • HER2/neu • histologic subtypes • normal tissue distribution • sarcoma • tumor distribution

Background

No molecule in the field of oncology has been more extensively or more successfully targeted for therapeutic intent than the product of the *c-erbB2* gene known as HER2/neu. The studies characterizing the basic biology of this molecule and its related family members were reviewed in Part I [1]. The HER2/neu molecule is expressed in a wide range of normal tissues, overexpressed in a variety of tumor types, with or without gene amplification, and is an established target for anti-tumor therapeutics. This review describes the distribution of HER2/neu expression in normal and developmental states, and describes tumor types that have HER2/neu overexpression and HER2/neu gene amplification, while addressing biological characteristics that impact the likelihood of success in translating any of the specific HER2/neu-targeted therapeutic strategies, described in Part I, into the clinical arena.

The normal expression of HER2/neu appears to be primarily transcriptionally regulated [2–7]. Expression of erbB2 has been detected in tissues derived from all three germ layers in both rat and human studies [8–14]. In rats, the erbB2 transcript was observed in embryonic yolk sac and placenta [13], in embryonic nervous tissue (E14, E16, but not E18 and beyond), in embryonic and early perinatal (PND-1) connective tissue, in both embryonic and adult skin, intestine, lung, kidney, but not in the spleen at any stage of development [12,15]. Generally, the level of expression of erbB2 mRNA was higher in embryonic tissues than in adult tissues [11,12]. In human samples, broad expression of erbB2 mRNA was observed in fetal tissues. In early embryos, transcript expression was observed in the placenta, the epithelium of the genitourinary tract (renal pelvis, ureter, fallopian tube, endometrium and endocervix), GI tract (oral cavity, esophagus, stomach, intestine and pancreas), pulmonary tract (trachea and bronchi) and adrenal medulla [8,10,14]. Interestingly, erbB2 mRNA was not detected in liver, nervous tissues including brain, striated and smooth muscle, endothelium or fibroblasts [8,10,14]. There is a notable difference in expression in the nervous system between rat and human embryonic tissues, once again

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demonstrating that there is incomplete concordance between rodents and humans at the genetic level. As in the rodent system, adult tissue expression levels are significantly lower than in early stages of development [16]. There is often concordant expression of other epidermal growth factor receptor family members in these tissues, see Table 1 for nomenclature. These expression patterns establish the potential for involvement of HER2/neu in a range of human neoplasms.

HER2/neu expression has been documented in a number of tumor types, in some cases accompanied by gene amplification (Table 2 & Box 1). Although gene amplification provides compelling evidence for biological significance, HER2 overexpression without gene amplification has also been associated with prognosis in multiple tumor types, potentially related to the transcriptional dysregulation or other mechanisms, as described in Part I [1]. Recently, there have been reports supporting biological functionality for cytoplasmic HER family members [17–19] including specifically HER2/neu [20–22] either of the full length form [23] or a amino-truncated, p95, fragment [24]. However, the clinical significance of overexpression of HER2/neu other than through signaling with other members of the EGFR family remains to be determined.

Breast

Initial studies characterizing the *erbB2* gene in human tumors, demonstrated that it was amplified in breast [25] and subsequently in ovarian carcinoma [26]. Slamon *et al.* and Berger *et al.* established the important poor prognostic characteristics of gene amplification of *c-erb B2* and associated overexpression of HER2/neu in breast cancer [25,27]. The situation in breast cancer is different from other tumor types in that the capacity to evaluate HER2/neu expression by immunohistochemistry (IHC) in a standardized manner, lagged behind the capacity to evaluate gene amplification, initially by Southern blot then fluorescent *in situ* hybridization. There were a number of antibodies raised against HER2/neu with widely variable reactivity in tissue sections [28–39]. In 1998, simultaneous with US FDA approval for trastuzumab (Herceptin®), Dako received approval for a commercial IHC kit, the Herceptest®. For several years there were competing strategies involving monoclonal or polyclonal antibodies. Subsequently it was demonstrated that a 3+ IHC score was associated with gene amplification in essentially 100% of cases, with a minority of cases with 2+ IHC score having gene amplification and essentially none case with 1+ IHC scores [40,41]. It is now widely acknowledged that approximately 30–45% of breast cancer cases demonstrate 2+ or 3+ IHC scores for membrane HER2/neu overexpression, with a fraction of those having gene amplification. Although there is a small percentage of hormone receptor-positive breast adenocarcinomas that also overexpress HER2/neu, the majority of hormone receptor-positive tumors do not overexpress HER2/neu [42,43]. Histologic subtypes such as mucinous, lobular and luminal A with high rates of hormone receptor expression very rarely overexpress HER2/neu [42,43]. Therefore, in adenocarcinoma of the breast, only a subset of tumors overexpressing HER2/neu exhibit gene amplification, approximately 20–25% [44–47]. Many practitioners rely on fluorescent *in situ* hybridization analyses to establish suitability for HER2/neu-targeted therapy for patients with breast cancer.

Gastric

c-erb-B2 gene expression is observed in fetal stomach [8] and 30–40% of gastric adenocarcinomas [48–64] overexpress HER2/neu. HER2/neu overexpression in gastric cancer has been documented to be a prognostic factor for gastric cancer [48–52]. Unlike breast cancer, HER2/neu overexpression does not appear to be a primary driver of gastric adenocarcinoma development and there has been significant controversy surrounding the incidence of HER2/neu overexpression, its biological importance, and its contribution to prognosis [49–64]. Recently, it has been appreciated that for gastric adenocarcinoma there is substantial intratumoral

Table 1. Nomenclature of EGF receptor family members.

Gene nomenclature	EGFR nomenclature	HER nomenclature	Common protein nomenclature	Kinase signaling capacity	Ligand(s)
erb-B1	EGFR	HER1	EGFR	Active	EGFR, amphiregulin, TGF-α, epigen, β-cellulin, HB-EGF
erb-B2	EGFR-2	HER2/neu	HER2/neu	Active	–
erb-B3	EGFR-3	HER3	EGFR-3	Inactive	Neuregulin 1, neuregulin 2
erb-B4	EGFR-4	HER4	EGFR-4	Active	Neuregulin 1, neuregulin 2, neuregulin 3, neuregulin 4, β-cellulin, HB-EGF

EGFR: EGF receptor.

Table 2. Tumors with HER2/neu overexpression.

Tumors type	Approximate frequency of overexpression (%)†	Approximate frequency of gene amplification (%)
Breast adenocarcinoma	17–35	15–25
Esophageal	≥30	15 to ≥30
Gastric	30–40	10–20
Colon	10–20	≤10–30‡
Pancreatic	20–30	2–16
Carcionoid, bowel (not gastric)	90	40
Lung, non-small-cell carcinoma	20–30	2–3
Head and neck	15–40	10–20
Salivary, mucoepidermoid adenocarcinoma	>75	50–80
Ovarian, epithelial	10–20	4–10
Ovarian, mucinous epithelial	18–35	16–18
Ovarian, Müllerian	40–52	68‡
Endometrial adenocarcinoma	16–52	3–63‡
Endometrial carcinosarcoma	20–30	14–43‡
Cervical squamous cell	10–30	14–17
Osteosarcoma	>40§	14–26
Synovial sarcoma	10–42	31‡
Transitional cell carcinoma	35	0–32
Prostate	55	<10
Thyroid, papillary	34–70	3–14
Meningioma	30 to >50	13
Gliomas	0–50	0
Childhood medulloblastomas	40–85	0¶
Wilms epithelial diffierentiation	>40	0

†Immunohistochemical scoring and primary antibodies vary, generally considered 3+ on a scale of 0–3. A small proportion of immunohistochemistry 2+ will also have gene amplification. Inclusion of immunohistochemistry 2+ as overexpression contributes to the high end of the ranges.
‡Gene amplification is reported to be more frequent than protein overexpression in some reports.
§A large proportion of tumors overexpress cytoplasmic HER2/neu with a smaller proportion <10% with membrane overexpression.
¶Only a single report describes evaluation of gene amplification and this report did not detect overexpressed protein.
NR: Not reported.

heterogeneity in the overexpression of HER2/neu and that some of the controversy may be related to sampling issues [63–69]. For gastric adenocarcinoma, there is controversy regarding cytoplasmic HER2/neu expression [70,71]. It is now well documented that there is an increased rate of HER2/neu overexpression in proximal gastric carcinomas, particularly of the intestinal histologic phenotype [72–75]. Despite the controversies surrounding the incidence and prognostic significance of HER2/neu overexpression, with or without gene amplification, the FDA approval of trastuzumab for the treatment of HER2/neu-positive gastric and gastroesophageal adenocarcinoma, and the adoption into national treatment guidelines [76,77], all but assures continued development of HER2/neu-targeted therapeutic strategies in HER2/neu overexpressing gastric and gastroesophageal cancers.

Esophagus & gastroesophageal junction

Similar to gastric cancers, HER2/neu overexpression is observed in >30% of esophageal neoplasms including Barrett's epithelium and adenocarcinoma [78–83]. The lower incidence of HER2/neu overexpression in Barrett's epithelium than in esophageal adenocarcinoma suggests that this defect is acquired later in the transformation process and may predict early transition from dysplasia to frank neoplasia [62,84,85]. Overexpression and prognostic significance is associated with HER2/neu overexpression, with and without gene amplification, in esophageal adenocarcinoma [78,80–83].

Box 1. Tumors without HER2/neu overexpression.

- Larynx
- Salivary (adenoidcystic)
- Lung, small cell
- Thymoma
- Peripheral neuroendocrine tumors, excluding small bowel carcinoid
- Ewings sarcoma
- Small bowel adenocarcinoma
- Anal carcinoma
- Hepatocellular
- Cholecysitic
- Renal cell carcinoma
- Germ cell neoplasms
- Common soft tissue sarcomas (rhabdomyo-, leiomyo-, fibro-, angio-, lipo-, chondro- sarcomas and malignant fibrous histiocytoma, among others)
- Desmoid
- Melanoma
- Basal cell carcinoma
- Lymphoma, non-Hodgkins and Hodgkin's
- Acute and chronic leukemias (myeloid and lymphoid)

Interestingly, a smaller but yet significant percentage of esophageal cancers with squamous cell histology also overexpress HER2/neu [86–88] and a recent preclinical study suggests that this histology may benefit from dual anti-HER1 and anti-HER2/neu antibody treatment [89]. In contrast to gastric adenocarcinoma, two studies suggest that in gastroesophageal junction (GE) adenocarcinoma there is less intratumoral variability and more concordance between primary and metastatic lesions in HER2/neu overexpression [62,65,66,90,91].

Pancreatic

Although expression of HER2/neu in fetal pancreatic exocrine or endocrine tissues has not been documented, HER2/neu overexpression is observed in pancreatic adenocarcinoma, averaging 20–30% [9,92–100], but possibly higher [100], ranging from no overexpression to 50%. A very limited proportion of tumors with HER2/neu overexpression are associated with gene amplification. This is complicated by the observation that HER2/neu expression decreases along the progression to poorly differentiated adenocarcinoma [101–103]. Therefore, it is no surprise that there is controversy as to whether HER2/neu overexpression represents a valid prognostic factor [104–106], be it a good [107] or a poor [100] prognostic factor. Proca *et al.* notes the challenge of background staining particularly in endocrine tissues and provides a potential source for the discrepancy in reports [108]. However, based on the experience with gastric and GE adenocarcinoma, HER2/neu might still be a viable target for pancreatic adenocarcinoma.

Hepatobiliary carcinomas: hepatocellular & cholangio carcinoma

Hepatocellular carcinoma is considered to have no HER2/neu overexpression [98,109–117], although there are groups who have reported a subset of hepatocellular carcinoma overexpressing HER2/neu [118–120]. The preponderance of evidence suggests that few if any hepatocellular carcinomas overexpress HER2/neu, either membrane or cytoplasmic [98,109–117]. As with pancreatic carcinoma, there is variability in the reporting of overexpression of HER2/neu in cholangiocarcinoma of the gall bladder [104,110,121–130]. It is notable that intrahepatic cholangiocarcinoma is a distinct entity that does have significant overexpression [104,122–125], but is generally included in the discussion of cholangiocarcinoma.

Intestine, colon & rectum

Colon adenocarcinoma is the most developed of these tumor types with respect to HER2/neu-targeted therapies, although most studies have not discriminated between colon and rectal adenocarcinoma. The consensus of the literature is that between 10 and 20% of adenocarcinomas overexpress HER2/neu in the colon [8,35,115,131–138] and in the rectum [139–143]. One source of the discrepancies in the reported expression or overexpression of HER2/neu is the presence of both cytoplasmic and membrane forms of HER2/neu [137,138]. The discrepancy in data as to HER2/neu overexpression in colorectal cancer contributes to the confusion as to whether HER2/neu is a poor prognostic factor and its role in the transformational process [144–148]. In studies examining rectal cancer, the data, although also mixed, suggests that HER2 overexpression is associated with a good prognosis [140–143]. As with many gastrointestinal tumors, there is a much lower frequency of gene amplification and thus, alternative mechanisms may lead to this aberrant expression of HER2/neu [2]. There is no evidence for HER2/neu overexpression in adenocarcinoma of the small intestine [149].

Lung

Similar to the upper GI tract, between 20 and 30% of non-small-cell carcinoma (NSCLC) of the lung have overexpression of HER2/neu [35,150–173], although also with a much lower frequency of gene amplification [35,174–176], implicating alternative mechanisms driving overexpression [177]. Small-cell carcinoma of the lung does not overexpress HER2/neu [151,153] and there is a recent report that supports only very rare cases of NSCLC with squamous cell histology having HER2/neu overexpression [178]. The expression pat-

tern and distribution of HER2/neu overexpression in NSCLC suggests that it is not directly involved in the transformation process of bronchial epithelium [179,180], as acquisition of HER2/neu overexpression follows disruption of p53 function and precedes acquisition of ras mutations [181]. Surprisingly, overexpression is associated with lower stage and grade of tumor [182]. Interestingly, there is an association of HER2/neu overexpression with NSCLC resistance to chemotherapy [183–191], which may account for the fact that HER2/neu overexpression is associated with a poor prognosis [35,160–173] despite the association of HER2/neu overexpression with lower stage and grade. There is evidence for cooperativity and co-expression of HER1/EGFR [192], potentially associated with poorer prognosis [161,169,193], and there is data to support overexpression of HER2/neu as a mechanism for resistance to antibody inhibition of HER1/EGFR [194]. Although, the co-expression of HER1/EGFR and HER2/neu is associated with increased effectiveness of HER1/EGFR-targeted tyrosine kinase inhibitors (e.g., gefitinib) [195,196] many of which also have inhibitory action on HER2/neu, as described in Part I [1], the presence of activating mutations in HER2/neu has been controversial, but the consensus is that there is a small population of HER2/neu expressing NSCLC, 2–4% of NSCLC, that can have a wide variety of HER2/neu mutations, primarily in the kinase domain, which constitute activating mutations [197–204] and that are exclusive of EGFR and RAS mutations [204–206]. HER2/neu mutations may be associated with resistance to some therapies [200–202]. Until recently it was widely held that unlike rat neu, in which an activating and transforming mutation in the transmembrane domain was originally noted, HER2/neu-positive tumors were driven by overexpression and not activating mutations.

Head & neck

Head and neck cancers including some salivary tumors (excluding adenoid cystic histology) have been variably reported to have HER2/neu expression across multiple subtypes (anatomic locations and histology). In the upper aerodigestive tract overexpression of HER2/neu has been reported in 15–25% of head and neck carcinomas [207–232], with the possible exception of laryngeal carcinomas [224,225]. Interestingly, in head and neck squamous cell carcinoma <7% of patients had membrane staining of HER2/neu [207]. The expression of HER2/neu is generally considered to be associated with a poor prognosis [228–233], although more recently this has come into question, at least for some subsets of head and neck cancer [226–228,234]. Gene amplification is a rare event, although it may be more frequent in certain subsets [235,236] or in recurrent disease [235]. Given the increasing prevalence of human papilloma virus (HPV)-positive head and neck cancers, it is of interest that there may be cooperativity between HER2/neu overexpression and HPV sequences in oncogenesis [237]. HER2/neu overexpression has been reported in >75% of salivary adenocarcinomas, including mucoepidermoid salivary gland tumors [208–233,238–241], with a high proportion of them being gene amplified [233,238–241], but not in the adenoid cystic histology [240–242]. Somewhat surprisingly, given the normal tissue and developmental distribution of HER2/neu, overexpression of HER2/neu has been reported in thyroid cancer of various histologies [243–245].

Nervous system

With the higher level of HER2/neu expression in fetal and developing tissues relative to the corresponding adult tissues, one might expect that the level of HER2/neu expression would be higher in more undifferentiated or high-grade CNS tumors, however this is not the case. HER2/neu overexpression has been reported in an overwhelming majority of meningiomas despite their well-differentiated state, low-grade growth characteristics and very low metastatic potential [246–250]. By contrast, HER2/neu expression or overexpression has been reported as nonexistent, as with the normal embryologic expression pattern, and in some reports in up to 50% of gliomas across the range from low-grade astrocytomas to glioblastoma multiforme [247,251–261] and a few activating mutations have been documented [262]. Interestingly, the special case of medulloblastoma, a subset of childhood nervous system tumors, has been documented to have a high proportion of overexpression of HER2/neu, with >30% of childhood medulloblastomas overexpressing HER2/neu [263,264].

Neuroendocrine tumors

Overexpression has been described in a high percentage of intestinal (nongastric) carcinoid tumors [265]. Although a small subset of carcinoid tumors arising outside of the colon have been variably described as overexpressing HER2/neu [105,266–271]. Some of these studies have used alternative antibodies to that employed by HercepTest™, therefore, accounting for some of the heterogeneity in the observed size of this subset. Given the rarity of these tumors and the small subset that overexpresses HER2/neu, it is unlikely that a clinical study of HER2/neu-targeted therapy will be undertaken in this setting. Other peripheral neuroendocrine tissues and tumors (e.g., PNET, pheochromocytoma, pancreatic endocrine and small-cell tumors of various organs) have not been demonstrated to express or overexpress HER2/neu.

Sarcomas

With the exception of osteosarcoma [272–287], synovial sarcoma [287–291], rhabdomyosarcoma [292–294], carcinosarcoma, and mixed Müllerian tumors, the latter two originating in the gynecologic tract that will be discussed below, there is no consistent evidence of HER2/neu expression or overexpression in the common soft tissue sarcomas [295–304]. HER2/neu is overexpressed in >40% of osteosarcomas [275,305], but is not a valid target in Ewings sarcoma [299,304,306] (consistent with the data above pertaining to lack of HER2/neu expression or overexpression in peripheral neuroendocrine tissues and tumors), chondrosarcomas or desmoid tumors [307]. There is a single, remote, unconfirmed report of non-AIDs related Kaposi's sarcoma having significant HER2/neu expression [308]. There is a very significant degree of cytoplasmic rather than membranous expression of HER2/neu in osteosarcoma and synovial sarcoma [283–288], probably accounting for some, if not all, of the discordance in reports of HER2/neu expression, similar to that described in colorectal adenocarcinomas [137,146]. Nevertheless, there have been two meta-analyses examining the literature regarding HER2/neu expression and prognosis in osteosarcoma that have concluded that there is substantial evidence for expression and that this expression is probably a poor prognostic factor [309,310]. Complicating the application of HER2/neu-targeted therapy is the observation that osteosarcomas downregulate expression of HER2/neu in metastatic lesions relative to the primary tumor [311].

Urinary tract

Normal kidney tissues, particularly the terminal collecting duct epithelium express HER2/neu [8,15,312]. Given the restriction of HER2 expression to transitional cell epithelium in the urinary system, it is somewhat surprising that renal carcinoma has been generally reported to have decreased expression of HER2/neu [225,312–318], which appears to vary inversely with the expression of HER1/EGFR [225,313], and there is no evidence of *HER2/neu* gene amplification [314]. Wilms tumors, which are thought to arise due to malignant transformation of residual renal stem cells, overexpress HER2/neu [319–322]. Based on the expression pattern of HER2/neu in normal kidneys it is no surprise that collecting duct and renal pelvic transitional cell carcinomas overexpress HER2/neu [323–328]. Transitional cell carcinoma (TCC) has been extensively examined for expression of HER2/neu. Although there is variability in the reported percentage of TCC that overexpress HER2/neu, the consensus resides in the 35–40% range [329–340]. HER2/neu overexpression is less common in superficial TCC [341] and lower grade tumors [335]. HER2/neu overexpression is associated with poor prognosis [332,342–344] and one third to one half of TCCs with overexpression have gene amplification [330,334,336,337].

Prostate

The study of HER2/neu-targeted therapies for prostate adenocarcinomas is complicated by the fact that normal prostatic epithelium expresses HER2/neu [345–347]. Therefore, it is not unexpected that there is a wide range of reported overexpression of HER2/neu in prostate adenocarcinoma, which extends from no overexpression [348] to 100% [349], averaging 55% for prostate carcinoma, including a recent meta-analysis [347–360]. The general consensus is that a substantial number of advanced prostate adenocarcinomas overexpress HER2/neu [347–349,353–360], with little or no gene amplification [358–364]. Variable expression of HER2/neu has been reported in prostate adenocarcinoma (none to 100%), HER2/neu overexpression is inversely correlated with Gleason Score and metastatic tumor [357–364]. Interestingly, although benign prostatic hypertrophy has not been reported to overexpress HER2/neu [351,352], it is expressed in the invasive cancer precursor, prostatic intraepithelial neoplasm at a level comparable to adenocarcinomas proper [347]. These data support a biological role for HER2/neu in malignant transformation of prostatic epithelium. Cross talk of the HER2/neu signaling pathways with androgen receptor activation and signaling has been described [365–372] in prostate adenocarcinoma, perhaps through mechanisms involving AKT, MAP kinase, and the PI3 kinase pathway [365–369] resulting in the stabilization of the androgen receptor [367,373]. This provides a framework for the involvement of HER family members, including HER2/neu, in the biology of androgen independent prostate cancer [374]. There has been a single report stating the HER2/neu expression is seen only in hormone responsive prostate cancer based on a sample set of 50 hormone-responsive and 25 hormone-resistant prostate cancer specimens [370]; however, this conflicts with the report of Reese *et al.* in which they describe 36% of their sample of hormone-independent prostate cancers expressing HER2/neu [358].

Gynecologic tumors

In addition to breast cancer, HER2/neu overexpression was recognized early in gynecologic neoplasms [125] including 10–20% of ovarian epithelial neoplasms [26,35,375–403]. Uterine carcinomas, specifically adenocarcinomas, are relatively uncommon tumors that overexpress HER2/neu. Reports of the percentage of endometrial adenocarcinomas that overexpress HER2/neu have ranged between 13% [377] and >50% [404,405] with

the consensus residing at approximately 20% [404–423], with approximately half of that percentage associated with gene amplification. However, there is not complete concordance between overexpression and gene amplification in endometrial adenocarcinoma [404–411,424,425]. Overexpression is generally associated with a poorer prognosis [405–409,412–414,426,427]. In endometrial adenocarcinoma the miRNA, miR-125b, inhibits the expression of HER2/neu and has been noted to be downregulated in HER2/neu-overexpressing endometrial adenocarcinoma samples [428]. Squamous cell carcinoma of the uterine cervix also expresses HER2/neu in 20–30% of the cases [10,377,415,429–437] with approximately 50–75% of those cases demonstrating gene amplification [438–442]. Gene amplification is positively associated with the presence of HPV-6, a low -risk HPV serotype, in the cervical biopsies [443]. Expression of HER2/neu in squamous cell carcinoma of the cervix has been associated with a poor prognosis [435–438,444] and an increased risk of recurrence after radiation therapy [444]. Carcinosarcoma has approximately the same percentage of HER2/neu overexpression as cervical squamous cell carcinoma despite its more aggressive clinical course [295,297,445–447] and this expression is closely associated with the carcinoma component [445,446]. Interestingly, the related mixed Müllerian tumors of the ovary demonstrate a much higher percentage of tumors with HER2/neu overexpression, 60% to nearly 100% [448–450].

Ovarian

Starting with the initial studies of Slamon *et al.* [26], the overexpression of HER2/neu has been described and extensively studied in ovarian cancer in parallel with breast adenocarcinoma [26,35,375–403]. The consensus supports HER2/neu overexpression in 10–20% of ovarian epithelial neoplasms [26,35,375–403]. The disparity in clinical success in targeting HER2/neu in ovarian epithelial tumors versus breast adenocarcinomas may be due to the fact that gene amplification drives a lower percentage of HER2/neu overexpression in ovarian epithelial neoplasms, occurring in less than half of the cases overexpressing HER2/neu [403,449,451–459] and the presence of cytoplasmic HER2/neu [395], which has been discussed above as a complicating factor in gastrointestinal, head and neck, lung and osteosarcoma. Additionally, there is some variability by histology [378–380,451,460], with recent data supporting a higher frequency of both gene amplification and HER2/neu overexpression in the mucinous subset of ovarian epithelial carcinomas [380–383] and in 60% to almost 100% of Müllerian tumors [448–450]. Generally, for ovarian epithelial neoplasms, HER2/neu overexpression or gene amplification is considered a poor prognostic factor [392–402,451,453], although not a particularly strong prognostic factor, and gene amplification may be a better prognostic indicator [453].

Miscellaneous tumors with HER2/neu overexpression

Owing to the fact that there is more pronounced expression of erbB2 in fetal or embryonic tissues, it is unexpected that there is only modest overexpression of HER2/neu in germ cell tumors and negligible gene amplification [461–463], >40%, in non-melanoma skin cancer [464] and in B lymphoblasts [465,466], but not in thymomas [467]. With the exceptions of the B lymphoblast, thymoma and variable sarcomas, tumors with HER2/neu overexpression arise from tissues that have been reported to have HER2/neu expression either in fetal or adult developmental stages.

Conclusion

HER2/neu is expressed and overexpressed in a broad range of normal tissues and tumor types, which are by and large concordant. However, the proportion of tumors with HER2/neu overexpression and gene amplification varies greatly by tumor type. Lessons learned from the work reviewed above reiterate a common theme in clinical research; the strategic selection of study populations, study end points, and careful matching of agent or strategy with the underlying biology within a given tumor type is critical for success. Although FDA approval of antibodies, antibody conjugates and tyrosine kinase inhibitors targeting HER2/neu has been obtained for breast, gastric and esophageal adenocarcinomas, there are other clear opportunities in other tumor types that have been identified. The basic science and preclinical work reviewed above substantiates the proposition that HER2/neu is an increasingly important therapeutic target.

Future perspective

The standardization and refinement of methodologies to assess HER2/neu overexpression and/or activation of its signaling pathway(s) will continue to define tumor types and subsets for which therapeutic targeting of HER2/neu is likely to be beneficial. Evolving systems biology approaches will provide additional information to identify target neoplasms for these therapies. The success of the targeted therapies for small molecularly defined tumor subsets, such as NSCLC with ALK activation (comprising ~4% of NSCLC adenocarcinomas), suggests that even for tumor types with a relatively low incidence or HER2/neu overexpression there will be subsets with the potential to benefit from therapies targeting HER2/neu. The advances in molecular diagnostics, systems biology and biological

network analyses will drive this process forward and provide a deeper understanding of which tumors have dysregulated HER activity. The major obstacle to be addressed and overcome is the ability to conduct meaningful clinical studies in rare subsets from tumor types that may be uncommon. Regulatory agencies and clinical leaders will have to address this issue for the field as a whole, not just for HER2/neu-overexpressing tumor subsets. Nevertheless, the next decade will see continued early-phase clinical studies of HER2/neu-targeted therapies, across the entire range of therapeutic agents in a multitude of tumor types with overexpression of HER2/neu or activation of the respective signaling pathway(s), which will be driven by advances in molecular/expression characterization of individual tumors.

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Executive summary

Distribution of HER2/neu expression in normal tissues

- Developmental associated expression
- Mature tissue expression

Distribution of HER2/neu expression in neoplastic tissues

- Breast
- Gastric
- Esophageal and gastroesophageal
- Pancreatic
- Hepatocellular and cholangiocarcinoma
- Small bowel, colon and rectum
- Lung
- Head and neck
- Nervous system
- Neuroendocrine
- Sarcomas
- Urinary tract
- Prostate
- Gynecologic tumors
- Miscellaneous tumors with HER2/neu expression
- Tumors without documented HER2/neu expression

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