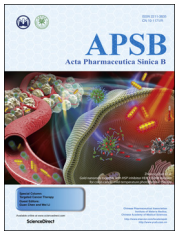
Acta Pharmaceutica Sinica B 2018;8(4):503–510

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Understanding the biology of HER3 receptor as a therapeutic target in human cancer

Hui Lyu, Amy Han, Erik Polsdofer, Shuang Liu, Bolin Liu*

Department of Pathology, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA

Received 21 March 2018; received in revised form 24 May 2018; accepted 28 May 2018

KEY WORDS

HER3;
Dimerization;
Cell signaling;
Therapeutic resistance;
Tumor metastasis;
Targeted therapy

Abstract HER3 belongs to the human epidermal growth factor receptor (HER) family which also includes HER1/EGFR/erbB1, HER2/erbB2, and HER4/erbB4. As a unique member of the HER family, HER3 lacks or has little intrinsic tyrosine kinase activity. It frequently co-expresses and forms heterodimers with other receptor tyrosine kinases (RTKs) in cancer cells to activate oncogenic signaling, especially the PI-3K/Akt pathway and Src kinase. Elevated expression of HER3 has been observed in a wide variety of human cancers and associates with a worse survival in cancer patients with solid tumors. Studies on the underlying mechanism implicate HER3 expression as a major cause of treatment failure in cancer therapy. Activation of HER3 signaling has also been shown to promote cancer metastasis. These data strongly support the notion that therapeutic inactivation of HER3 and/or its downstream signaling is required to overcome treatment resistance and improve the outcomes of cancer patients.

Abbreviations: Ab, antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; FDA, Food and Drug Administration; HER, Human epidermal growth factor receptor; HRG, heregulin; IGF-1R, insulin-like growth factor-I receptor; lncRNA, long ncRNA; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; miRNA, microRNA; ncRNA, noncoding RNA; NSCLC, non-small cell lung cancer; OS, overall survival; PI-3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor

*Corresponding author.
E-mail address: bolin.liu@ucdenver.edu (Bolin Liu).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

https://doi.org/10.1016/j.apsb.2018.05.010

1. Introduction

Human epidermal growth factor receptor (HER) family includes the epidermal growth factor receptor (EGFR), HER2 (also known as erbB2/*neu*), HER3 (erbB3), and HER4 (erbB4). It is arguably the most important family of receptor tyrosine kinase (RTK) in normal development and tumorigenesis[1,2]. These receptors are widely expressed in epithelial, mesenchymal, and neuronal cells[3]. Abnormal expression of HER family members is involved in carcinogenesis and progression of diverse types of human cancer[4,5]. While EGFR, HER3, and HER4 have ligands, HER2 has no known ligand. When a ligand binds to the extracellular region of EGFR, HER3, or HER4 (domains I and III), the dimerization arm in domain II is exposed leading to receptor-receptor interaction[6]. Dimerization is an essential step for the receptor function and activation of the cytoplasmic signaling, including PI-3K/Akt, MEK/MAPK, Jak/Stat pathways, Src kinase, etc.[5,7]. EGFR, HER3, and HER4 normally exist as inactive molecularly folded monomers to prevent dimerization[8,9], whereas HER2 is always in a constitutively active conformation with its dimerization arm opening even without ligand binding[8]. Accumulating evidence indicates that HER3 frequently co-expresses and interacts with other RTKs to form a heterodimeric complex, which subsequently activates oncogenic signaling, especially the PI-3K/Akt pathway and Src kinase to promote cancer cell survival, proliferation, and progression[10–12]. Studies on the underlying mechanisms demonstrate that HER3 signaling plays a major role causing treatment failure in cancer therapy[13,14]. Recent reports reveal that enhanced HER3 signaling facilitates tumor cell motility and intravasation in breast cancer lung metastasis[15]; and a HER3-lncRNA (long noncoding RNA) axis regulates bone metastasis in breast cancer[16,17]. Increased expression and activation of HER3 has also been observed in brain metastasis of breast cancer resistance to PI-3K inhibition[18,19]. Collectively, these data support the importance of developing effective therapeutics to inhibit HER3 signaling for cancer treatment. A number of anti-HER3 monoclonal antibodies are actively under preclinical studies and clinical evaluation in cancer patients. There is currently no HER3-targeted therapy approved by the FDA for cancer treatment. This review summarizes our understanding of the unique biology of HER3 in cancer progression and discusses the latest advances in identifying therapeutic antibodies against HER3 for cancer treatment.

2. Unique biology of HER3-initiated signaling in human cancer

HER3 is a unique member of the HER family as it has been considered as an inactive receptor[20,21], although a recent study suggests that HER3 contains weak kinase activity[22]. Sequence comparison of tyrosine kinase domains among the HER receptors reveals that certain residues, including Cys-721, His-740, and Asn-815, in HER3 have non-conservative substitutions. These changes significantly reduce the kinase activity of HER3[23]. Thus, to fully transduce signaling, HER3 has to form dimers with other receptors and be phosphorylated by its interactive partners, with HER2 being the most important one[24]. Of the four HER receptors, HER3 is best suited to induce activation of the PI-3K/Akt pathway, which is a well-known survival signaling pathway in normal development and tumorigenesis[25]. This is likely due to the C-terminal tail of HER3 having multiple tyrosine residues, whose phosphorylation is able to bind to the p85 subunit of PI-3K[24]. It is thought that, among all the homo- and hetero-dimerization complexes potentially formed by HER receptors, the HER2/HER3 heterodimer is the most biologically active and potent to activate the PI-3K/Akt signaling cascade[26,27].

Overexpression of HER3 is frequently observed in a wide variety of human malignancies, including colorectal carcinoma, head and neck squamous cell carcinoma, melanoma, and breast, gastric, ovarian, prostate, and bladder cancers[28–30]. Moreover, it has been shown that HER3 is a more potent partner than other HER receptors for the oncogenic activity of HER2 in HER2-overexpressing tumors[29,31–33]. Especially in *erbB2*-amplified breast cancers, preferential phosphorylation of HER3, but not EGFR, is found[29]. Indeed, most metastatic breast cancers have expression of either EGFR or HER2, and rarely express both[34]. In contrast, HER2 and HER3 commonly co-express in breast cancer tissues[35] and breast cancer cell lines[36]. Elevated expression of the endogenous mouse HER3 and its association with the transgene encoded erbB2 promote mammary tumorigenesis in *erbB2/neu*-transgenic mice[37,38]. Despite its lack of[20,21] or weak kinase activity[22], HER3 serves as a critical co-receptor of HER2 and its expression is essential for HER2-mediated breast cancer cell survival and proliferation[10,11]. These data have been supported by a recent meta-analysis of 12 clinical studies of human cancers, including colorectal cancer, gastric cancer, breast cancer, melanoma, ovarian cancer, head and neck cancer, pancreatic cancer, and cervical cancer[39]. It concludes that expression of HER3 is associated with worse survival in solid tumors, and the impact of HER3 on clinical outcome is greater in those tumors where HER2 is also overexpressed[39].

Overexpression of HER3 has been reported in 50%–70% of human breast cancers[40–42] and appears to be associated with prognostic factors, such as distant metastasis, tumor size, risk of local recurrence, and etc.[43,44], although the prognostic value of HER3 in breast cancer is not well documented and the currently available data are inconsistent[42–46]. Some studies show that elevated expression of HER3 significantly correlates with reduced overall survival and disease-free survival[35,47,48], whereas others report HER3 expression as a favorable prognostic factor of overall survival in breast cancer patients[49,50]. Several theories have been proposed to explain the controversial findings, such as the potential influence of HER3 ligand—heregulin (HRG) and subcellular distribution of HER3[14]. The fact that we do not have a unified methodology to detect HER3 expression in clinical samples may also account for the inconsistent data, as each laboratory uses different antibodies and probes to detect the expression of HER3 protein and mRNA. In addition, breast cancer is a heterogenous disease with several intrinsic subtypes, including luminal, HER2-enriched, and triple negative breast cancer (TNBC)[51]. It is possible that HER3 exhibits distinct influences on patient survival in different subtypes of breast cancer. Thus, detailed evaluation of HER3 expression and its interactive partners in a specific subtype is warranted to define the prognostic value of HER3 signaling in such subtype of breast cancer patients.

3. Mechanism of HER3-mediated cancer progression

Accumulating evidence emphasizes the critical role of HER2/HER3 heterodimer-mediated PI-3K/Akt signaling in cancer development[39,52]. Basic research on the underlying mechanisms indicates that HER2 contributes to breast carcinogenesis potentially

via two major mechanisms—increased therapeutic resistance and enhanced metastatic potential[53,54]. Thus, it is conceivable to hypothesize that HER3 signaling-mediated cancer progression is likely through its capability to induce therapeutic resistance and promote tumor metastasis.

3.1. *HER3 and cancer treatment resistance*

A recent report implicates HER3 activation as a major cause of treatment failure in cancer therapy[13]. It has been shown that HER3 signaling plays a crucial role in the development of various human cancers, including HER2-overexpressing breast cancer[10,11], castration-resistant prostate cancer[55], platinum-resistant/refractory ovarian cancer[56,57], and non-small cell lung cancer (NSCLC) resistance to EGFR tyrosine kinase inhibitor (TKI)[58,59]. A number of studies reveal that compensatory upregulation of HER3 along with the sustained PI-3K/Akt signaling is implicated as an important mechanism resulting in resistance to EGFR-targeted therapy[60–63]. In addition, elevated expression of the HER3 ligand (HRG) is a possible mechanism of resistance to anti-EGFR antibody (Ab)-cetuximab in the treatment of patients with colorectal cancer[64]. Furthermore, HER3 may work in concert with other RTKs, such as hepatocyte growth factor receptor (HGFR or MET)[65]. Amplification of *MET* oncogene may also result in resistance to EGFR-TKI (gefitinib). Phosphorylated HER3 was able to interact with the p85 subunit of PI-3K in a MET kinase-dependent manner in NSCLC, suggesting a role of HER3 in MET-induced resistance to gefitinib[65]. In squamous cell carcinomas of head and neck cancer cell lines sensitive to the dual EGFR/HER2 inhibitor lapatinib, increased HRG and activated HER3 strongly correlated with lapatinib sensitivity[66]. However, the potential mechanism by which HER3 may be a valuable biomarker for lapatinib sensitivity and gefitinib resistance remains unclear. It may be through distinct activation mechanisms that need to be further investigated.

Studies in our laboratory have been focusing on the biologic function of HER3 in the progression of *erbB2*-aberrant breast cancer. We show that elevated expression of HER3 in HER2-overexpressing breast cancer cells results in resistance to hormone therapy (tamoxifen), HER2-targeted therapy (trastuzumab and lapatinib), and chemotherapy (paclitaxel)[67–71]. Our data demonstrate the crucial role of HER3 signaling in HER2-mediated therapeutic resistance to tamoxifen, trastuzumab, and paclitaxel in breast cancer[12,14]. One innovative finding comes from our studies on the underlying mechanism of HER3-mediated resistance to the anti-HER2 antibody trastuzumab (also known as Herceptin). It was reported that both HER3 and the insulin-like growth factor-I receptor (IGF-1R)-mediated signaling contributed to trastuzumab resistance[72–74], whereas the relationship between HER3 and IGF-IR in trastuzumab resistance was less understood. Our studies uncovered that HER2 interacted with both HER3 and IGF-1R to form a heterotrimeric complex in the trastuzumab-resistant breast cancer cells we tested. In fact, it was the heterotrimer of HER2/HER3/IGF-1R, not the heterodimer of HER2/HER3 or IGF-1R/HER2, that played a causal role leading to trastuzumab resistance[67]. Further studies on downstream signaling revealed that HER3 and IGF-1R triggered different signaling pathways contributing to trastuzumab resistance - HER3 activated both PI-3K/Akt signaling and Src kinase, whereas IGF-1R mainly elicited Src activation[67]. Interestingly, our recent data show that HER3 and IGF-1R exhibit distinct effects on the sensitivity of HER2-overexpressing breast cancer cells to lapatinib, another HER2-targeted therapy[71]. While HER3 signaling also induces lapatinib resistance in the trastuzumab-resistant breast cancer cells, IGF-1R signaling did not alter lapatinib sensitivity[71].

3.2. *HER3 and tumor metastasis*

HER3 frequently co-expresses and interacts with HER2 to activate oncogenic signaling, especially the PI-3K/Akt pathway and Src kinase, and promote cancer cell survival, proliferation, and progression[10–12]. We have shown that elevated expression of HER3 confers resistance to several commonly used therapeutics against HER2-overexpressing breast cancer[67–71]. Drug-resistant tumors likely recur and metastasize to distant organs. Thus, it is generally believed that overexpression of HER3 and its downstream signaling can promote tumor metastasis. Activation of HER3 signaling facilitates tumor cell motility and intravasation in lung metastasis of human breast cancer[15]. Our analysis of clinical database reveals that increased HER3 expression leads to a worse overall survival (OS) in lymph node positive breast cancer patients. Especially in HER2-overexpressing breast cancer, the patients with higher expression of HER3 show poorer OS and distant metastasis-free survival (Liu laboratory unpublished data). In addition, the HER3 ligand, HRG can stimulate chemotaxis and invasion *via* HER2/HER3 heterodimers[75]. Recent studies suggest that the HRG-HER3 signaling axis plays a crucial role in the brain metastasis of breast cancer[18,19]. While overexpression of HER3 is found in the brain metastatic legions of breast cancer[19,76], activation of HER3 and its downstream signaling has also been observed in breast cancer brain metastasis likely *via* increased HRG production by the stromal cells in brain microenvironment[18,19,77]. Activation of the downstream signaling, such as the PI-3K/Akt and MEK/MAPK pathways can be critical for cell motility and chemotaxis[75,78–82]. PI-3K is capable of regulating cytoskeleton through Rho family G proteins and Akt activation[83–85]. MAPKs can influence adhesion dynamics directly and control gene expression patterns essential for motility and invasion[86–88]. It is possible that HER3-dependent motility contributes to cancer metastasis independent of its effects on tumor growth[89]. Studies on the underlying mechanisms involved in ovarian cancer spread to the omentum shows that elevated expression of HER3 in ovarian cancer cells and increased HRG in the omentum allows for cancer cell localization and growth in the omentum. These findings suggest that the HRG-HER3 signaling axis is also a dominant mechanism responsible for ovarian cancer metastasis *via* blood stream[90].

Interestingly, noncoding RNA (ncRNA), including the long ncRNA (lncRNA) MAYA also plays an important role in HER3-mediated tumor metastasis[17]. It has been reported that a ROR1-HER3-lncRNA axis regulates bone metastasis in breast cancer[16,17]. In our efforts to identify key downstream mediators of HER3 signaling in breast cancer metastasis, we found that HER3 signaling specifically downregulates expression of the tumor suppressive miR-203 and miR-542-3p in HER2-overexpressing breast cancer cells[91]. Bioinformatics analyses reveal that miR-203 and miR-542-3p target several genes, including *Survivin, ZEB1*, *ZEB2*, *Snail1,* and/or *Slug*, which are critical for drug resistance, epithelial-mesenchymal transition (EMT), and tumor metastasis (Liu's laboratory unpublished data). These data support the notion that HER3 signaling regulates expression of lncRNAs and miRNAs to promote cancer metastasis. Studies in this innovative area will not only further our understanding of HER3 signaling in cancer biology, but may also provide a new

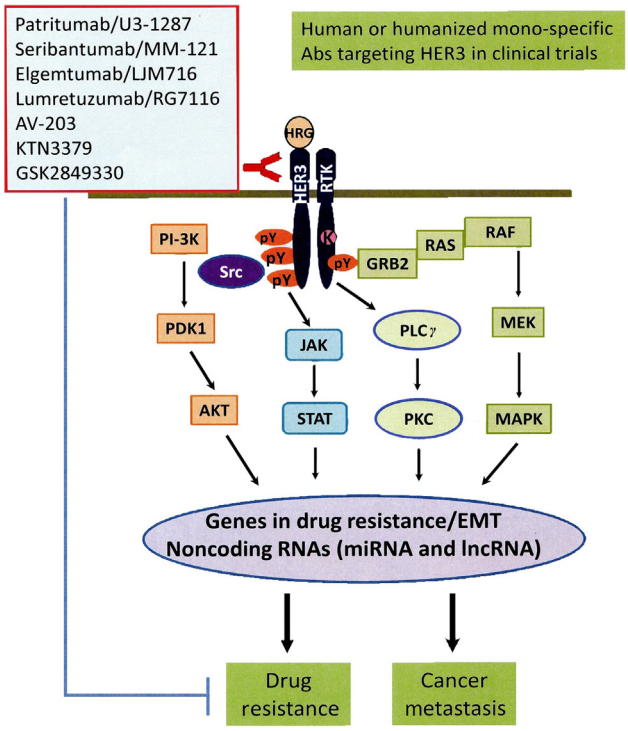


Figure 1 A diagram showing the major signaling pathways of HER3 during cancer progression and the mono-specific HER3 blocking Abs currently in clinical trilas of cancer patients. The ligand, HRG bound HER3 recruits another RTK to form a heterodimer, which subsequently triggers activation of multiple signaling pathways, including PI-3K/Akt, MEK/MAPK, Jak/Stat pathways, and Src kinase. The downstream signaling will further induces expression of a cohort of crucial genes responsible for drug resistance and cancer metastasis. HER3 signaling is also able to regulate expression of some ncRNAs, including miRNAs and lncRNAs. Currently, there are several human or humanized anti-HER3 mono- and bi-specific Abs in clinical trilas testing their therapeutic activity to abrogate drug resistance and inhibit cancer metastasis.

avenue for identification of novel therapeutic approaches to abrogate HER3-mediated treatment resistance and tumor metastasis. Figure 1 shows a simple diagram depicting that activation of HER3 and its major downstream signaling induces expression of a cohort of critical molecules, including some EMT markers and ncRNAs, responsible drug resistance and cancer metastasis.

4. Therapeutic antibody against HER3 for cancer treatment

Elevated expression of HER3 plays an essential role in human cancer progression and correlates with a worse overall survival in many solid tumors[13,25,39], emphasizing the importance in developing novel effective strategic targeting of HER3[14,52,92]. Inhibition of HER3 is believed to be required to overcome resistance and effectively treat cancer patients. Because of its lack of or low kinase activity[21,22], targeting HER3 with a blocking Ab is the only strategy under preclinical studies[93,94] and clinical evaluations in patients with advanced solid tumors (http://www.clinicaltrials.gov). Advances have been made to identify HER3-targeted therapy[95], and several anti-HER3 monoclonal Abs exhibit antitumor activity *in vivo* and show promise as novel cancer therapeutics[96,97]. Recent studies have identified bispecific Abs dual-targeting EGFR/HER3[59] or HER2/HER3[98], that exert potent antitumor activities in both laboratory studies and clinic testing[95]. The HER3 inhibitors based on a novel biologic scaffold termed surrobody have been developed and display anti-proliferative effects on cancer cells *in vitro* and *in vivo*[99].

MM-121 (also known as seribantumab, Merrimack Pharmaceuticals, Cambridge, MA), a human anti-HER3 monoclonal IgG2 Ab, blocks ligand-induced HER2/HER3 dimerization and subsequently inhibits downstream signaling. MM-121 exerts antitumor activity in preclinical studies of various human cancers[93,94]. We have tested the hypothesis that MM-121 may be able to abrogate HER3 signaling-mediated resistance to trastuzumab and paclitaxel in HER2-overexpressing breast cancer cells *via* inactivation of HER3 and its downstream PI-3K/Akt signaling. We reported that MM-121 was able to overcome paclitaxel resistance and significantly enhanced paclitaxel-induced apoptosis in the otherwise resistant breast cancer cell lines[100]. We also showed that MM-121 dramatically inhibited PI-3K/Akt signaling in HER2-overexpressing breast cancer cells refractory to trastuzumab, and significantly enhanced trastuzumab-induced growth inhibition[101]. MM-121 in combination with trastuzumab mainly induced cell cycle G1 arrest *in vitro*, whereas the combinations of MM-121 and trastuzumab potently inhibited tumor growth *in vivo* likely due to induction of both growth inhibition and apoptosis[101]. Our data strongly support the initiation of clinical trials to evaluate the efficacy of MM-121 in combination with trastuzumab or paclitaxel in HER2-overexpressing breast cancer patients who have developed resistance to the therapeutics. Interestingly, recent studies suggest that higher HRG mRNA expression and low HER2 levels predict a clinical benefit from the addition of seribantumab (MM-121) to standard of care therapies in patients with platinum-resistant/refractory ovarian cancer, hormone receptor-positive HER2-negative breast cancer, and EGFR wild-type NSCLC[102,103]. MM-111 (Merrimack Pharmaceuticals, Cambridge, MA) is a bispecific antibody, dual-targeting HER2/HER3, inhibiting the PI-3K/Akt signaling[98]. The safety and clinical activity of MM-111 is now being tested in several phase I clinical trials. Another HER3-targeted drug, U3–1287/AMG-888 (originally developed by Amgen Inc., Thousand Oaks, CA; later acquired by Daiichi Sankyo Co., Ltd., Tokyo, Japan and re-named as patritumab) is the first fully human anti-HER3 monoclonal Ab and currently under phase III clinical investigations in patients with advanced solid tumors[104]. This Ab has been shown to inhibit proximal and distal HER signaling and induces rapid internalization of HER3[105]. Patritumab induces growth inhibition in various cancer cell lines (breast, lung, colorectal) that are resistant to other HER inhibitors[105]. It significantly decreases colony formation in pancreatic cancer cells and tumor growth in tumor xenograft models of pancreatic cancer, NSCLC, and colorectal cancer[55]. Interestingly, patritumab is also able to overcome HRG-dependent resistance to EGFR inhibitors in NSCLC *in vitro* and *in vivo*, suggesting that patritumab may be useful in combination with EGFR TKIs, such as erlotinib to treat the NSCLC patients with high expression of HRG[106,107]. Lumretuzumab (RG7116) is a humanized anti-HER3 IgG1 monoclonal Ab developed by Roche Diagnostics GmbH (Penzberg, Germany). It binds to the extracellular domain of HER3 with high affinity to prevent HRG binding[108]. As a glycoengineered monoclonal Ab, lumretuzumab displayed an enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity as compared with the non-glycoengineered parental antibody[109]. Although lumretuzumab was well tolerated and showed

evidence of clinical activity in a phase I trial[110], two recent phase Ib studies suggest otherwise. The toxicity profile of lumretuzumab in combination with the EGFR-targeted therapies cetuximab and erlotinib was managable, but it exerted little clinical benefit in various cancers[111]. The therapeutic window of lumretuzumab in combination with the anti-HER2 Ab pertuzumab and chemotherapeutic drug paclitaxel for HER3-positive metastatic breast cancer was too narrow to warrant further clinical development[112]. Several anti-HER3 mono-specific Abs currently under clinical trials with a hope to abrogate HER3-mediated drug resistance and cancer metastasis are shown in Figure 1. Recently, a new anti-HER3 Ab (MP-RM-1) and its humanized version (EV20) exhibit potent antitumor effects in several cancer types *in vitro* and *in vivo*[113,114]. Because of EV20's capability to inhibit both ligand-dependent and -independent activation of HER3[113,114], it is speculated that EV20 may have a broader effect on blocking HER3 signaling than the Abs (like MM-121) which can only block ligand-induced HER3 activation.

5. Perspectives

Research on HER receptors has been focusing on the dysregulation of EGFR and HER2 in human malignancies. The importance of HER3 as an obligate partner for receptor dimerization and in resistance to HER2- or EGFR-targeted therapy and other therapeutics has drawn a lot of attention to define HER3 as a molecular target for cancer treatment. Increased awareness of HER3 function in drug resistance and tumor metastasis has critical implications in the directions of future studies. First, the crucial downstream mediators of HER3 signaling in cancer progression remain elusive. Basic research deciphering the molecular basis of HER3-mediated drug resistance and tumor metastasis is essential to improve our understanding of the unique biology of HER3 in human cancer. Such studies will also facilitate the development of novel therapeutic approaches inhibiting the key downstream mediators against those cancers driven by HER3 signaling. Second, although several anti-HER3 Abs are actively under clinical evaluations in various human cancers, to date no HER3-targeted therapy has been approved by the FDA for cancer treatment. This is possibly due to the uniqueness of HER3 receptor, which may influence the antitumor activity of anti-HER3 Abs. Since HER3 has to form heterodimer or heterotrimer complexes with other RTKs in order to fully transduce signaling[10,11,67], anti-HER3 monotherapy is unlikely to show significant efficacy against human cancer. We must consider effective combination strategies with a HER3-targeted therapy plus other targeted therapies or chemotherapeutic agents for cancer treatment. Third, it has been shown that HRG expression at tumor sites predicts efficacy of seribantumab (MM-121) in the treatment of human cancers[102,103], suggesting that identification of predictive biomarkers will stratify the usage of anti-HER3 Abs for effective cancer treatment. Indeed, a new anti-HER3 Ab, 9F7-F11, which does not compete with the ligand (HRG), shows higher efficacy than the Abs that compete with the ligand for binding to HER3[115]. In human tumor cell xenograft models, 9F7-F11 exerts an enhanced antitumor activity in the presence of HRG and thus represents a novel treatment strategy for HRG-addicted tumors[115]. We believe that HER3 is a focal point in HER receptors-mediated tumorigenesis and plays an essential role in cancer progression. Thus, HER3 constitutes a unique biomarker and molecular target for effective treatment of human cancer.

Acknowledgments

This work was supported in part by a grant from the National Institutes of Health (NIH), USA (R01CA201011 to BL) and a grant from the National Natural Science Foundation of China (81472763 to BL).

References

1. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer* 2009;**9**:463–75.
2. Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol* 2009;**21**:177–84.
3. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer* 2005;**5**:341–54.
4. DeFazio A, Chiew YE, Sini RL, Janes PW, Sutherland RL. Expression of c-erbB receptors, heregulin and oestrogen receptor in human breast cell lines. *Int J Cancer* 2000;**87**:487–98.
5. Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J* 2000;**19**:3159.
6. Ogiso H, Ishitani R, Nureki O, Fukai S, Yamanaka M, Kim J-H, et al. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. *Cell* 2002;**110**:775–87.
7. Ferguson KM, Berger MB, Mendrola JM, Cho H-S, Leahy DJ, Lemmon MA. EGF activates its receptor by removing interactions that autoinhibit ectodomain dimerization. *Mol Cell* 2003;**11**:507–17.
8. Burgess AW, Cho H-S, Eigenbrot C, Ferguson KM, Garrett TP, Leahy DJ, et al. An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors. *Mol Cell* 2003;**12**:541–52.
9. Cho H-S, Leahy DJ. Structure of the extracellular region of HER3 reveals an interdomain tether. *Sci Signal* 2002;**297**:1330–3.
10. Holbro T, Beerli RR, Maurer F, Koziczak M, Barbas 3rd CF, Hynes NE. The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: erbb2 requires ErbB3 to drive breast tumor cell proliferation. *Proc Natl Acad Sci U S A* 2003;**100**:8933–8.
11. Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoeflich KP, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res* 2008;**68**:5878–87.
12. Lee Y, Ma J, Lyu H, Huang J, Kim A, Liu B. Role of erbB3 receptors in cancer therapeutic resistance. *Acta Biochim Biophys Sin (Shanghai)* 2014;**46**:190–8.
13. Amin DN, Campbell MR, Moasser MM. The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics. *Semin Cell Dev Biol* 2010;**21**:944–50.
14. Ma J, Lyu H, Huang J, Liu B. Targeting of erbB3 receptor to overcome resistance in cancer treatment. *Mol Cancer* 2014;**13**:105.
15. Xue C, Liang F, Mahmood R, Vuolo M, Wyckoff J, Qian H, et al. ErbB3-dependent motility and intravasation in breast cancer metastasis. *Cancer Res* 2006;**66**:1418–26.
16. Li C, Wang S, Xing Z, Lin A, Liang K, Song J, et al. A ROR1-HER3-lncRNA signalling axis modulates the Hippo-YAP pathway to regulate bone metastasis. *Nat Cell Biol* 2017;**19**:106–19.
17. Zhuo W, Kang Y. Lnc-ing ROR1-HER3 and Hippo signalling in metastasis. *Nat Cell Biol* 2017;**19**:81–3.
18. Kabraji S, Ni J, Lin NU, Xie S, Winer EP, Zhao JJ. Drug resistance in HER2-positive breast cancer brain metastases: blame the barrier or the brain?. *Clin Cancer Res* 2018;**24**:1795–804.
19. Kodack DP, Askoxylakis V, Ferraro GB, Sheng Q, Badeaux M, Goel S, et al. The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation. *Sci Transl Med* 2017;**9**:eaal4682.
20. Boudeau J, Miranda-Saavedra D, Barton GJ, Alessi DR. Emerging roles of pseudokinases. *Trends Cell Biol* 2006;**16**:443–52.
21. Citri A, Skaria KB, Yarden Y. The deaf and the dumb: the biology of ErbB-2 and ErbB-3. *Exp Cell Res* 2003;**284**:54–65.

22. Shi F, Telesco SE, Liu Y, Radhakrishnan R, Lemmon MA. ErbB3/HER3 intracellular domain is competent to bind ATP and catalyze autophosphorylation. *Proc Natl Acad Sci U S A* 2010;**107**:7692–7.
23. Plowman GD, Whitney GS, Neubauer MG, Green JM, McDonald VL, Todaro GJ, et al. Molecular cloning and expression of an additional epidermal growth factor receptor-related gene. *Proc Natl Acad Sci U S A* 1990;**87**:4905–9.
24. Schulze WX, Deng L, Mann M. Phosphotyrosine interactome of the ErbB-receptor kinase family. *Mol Syst Biol* 2005;**1**(2005)0008.
25. Campbell MR, Amin D, Moasser MM. HER3 comes of age: new insights into its functions and role in signaling, tumor biology, and cancer therapy. *Clin Cancer Res* 2010;**16**:1373–83.
26. Mattoon D, Lamothe B, Lax I, Schlessinger J. The docking protein Gab1 is the primary mediator of EGF-stimulated activation of the PI-3K/Akt cell survival pathway. *BMC Biol* 2004;**2**:24.
27. Suenaga A, Takada N, Hatakeyama M, Ichikawa M, Yu X, Tomii K, et al. Novel mechanism of interaction of p85 subunit of phosphatidylinositol 3-kinase and ErbB3 receptor-derived phosphotyrosyl peptides. *J Biol Chem* 2005;**280**:1321–6.
28. Beji A, Horst D, Engel J, Kirchner T, Ullrich A. Toward the prognostic significance and therapeutic potential of HER3 receptor tyrosine kinase in human colon cancer. *Clin Cancer Res* 2012;**18**:956–68.
29. Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoeflich KP, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res* 2008;**68**:5878–87.
30. Maurer CA, Friess H, Kretschmann B, Zimmermann A, Stauffer A, Baer HU, et al. Increased expression of erbB3 in colorectal cancer is associated with concomitant increase in the level of erbB2. *Human Path* 1998;**29**:771–7.
31. Alimandi M, Romano A, Curia MC, Muraro R, Fedi P, Aaronson SA, et al. Cooperative signaling of ErbB3 and ErbB2 in neoplastic transformation and human mammary carcinomas. *Oncogene* 1995;**10**:1813–21.
32. Hsieh A, Moasser M. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer* 2007;**97**:453–7.
33. Wallasch C, Weiss F, Niederfellner G, Jallal B, Issing W, Ullrich A. Heregulin-dependent regulation of HER2/*neu* oncogenic signaling by heterodimerization with HER3. *EMBO J* 1995;**14**:4267–75.
34. Grupka NL, Lear-Kaul KC, Kleinschmidt-DeMasters BK, Singh M. Epidermal growth factor receptor status in breast cancer metastases to the central nervous system. Comparison with HER-2/neu status. *Arch Pathol Lab Med* 2004;**128**:974–9.
35. Bieche I, Onody P, Tozlu S, Driouch K, Vidaud M, Lidereau R. Prognostic value of ERBB family mRNA expression in breast carcinomas. *Int J Cancer* 2003;**106**:758–65.
36. deFazio A, Chiew YE, Sini RL, Janes PW, Sutherland RL. Expression of c-erbB receptors, heregulin and oestrogen receptor in human breast cell lines. *Int J Cancer* 2000;**87**:487–98.
37. Siegel PM, Ryan ED, Cardiff RD, Muller WJ. Elevated expression of activated forms of *Neu*/ErbB-2 and ErbB-3 are involved in the induction of mammary tumors in transgenic mice: implications for human breast cancer. *EMBO J* 1999;**18**:2149–64.
38. Kim A, Liu B, Ordonez-Ercan D, Alvarez KM, Jones LD, McKimmey C, et al. Functional interaction between Mouse erbB3 and wild type rat c-neu in transgenic mouse mammary tumor cells. *Breast Cancer Res* 2005;**7**:R708–18.
39. Ocana A, Vera-Badillo F, Seruga B, Templeton A, Pandiella A, Amir E. HER3 overexpression and survival in solid tumors: a meta-analysis. *J Natl Cancer Inst* 2013;**105**:266–73.
40. Barnes NL, Khavari S, Boland GP, Cramer A, Knox WF, Bundred NJ. Absence of HER4 expression predicts recurrence of ductal carcinoma *in situ* of the breast. *Clin Cancer Res* 2005;**11**:2163–8.
41. Naidu R, Yadav M, Nair S, Kutty M. Expression of c-erbB3 protein in primary breast carcinomas. *Br J Cancer* 1998;**78**:1385–90.
42. Quinn C, Ostrowski J, Lane S, Loney D, Teasdale J, Benson E. c-erbB-3 protein expression in human breast cancer: comparison with other tumour variables and survival. *Histopathology* 1994;**25**:247–52.
43. Lemoine N, Barnes D, Hollywood D, Hughes C, Smith P, Dublin E, et al. Expression of the ERBB3 gene product in breast cancer. *Br J Cancer* 1992;**66**:1116–21.
44. Travis A, Pinder S, Robertson J, Bell J, Wencyk P, Gullick W, et al. C-erbB-3 in human breast carcinoma: expression and relation to prognosis and established prognostic indicators. *Br J Cancer* 1996;**74**:229–33.
45. Gasparini G, Pozza F, Bevilacqua P, Gullick W, Lemoine N, Maluta S, et al. c-erbB-3 and c-erbB-2 protein expression in node-negative breast carcinoma—an immunocytochemical study. *Eur J Cancer* 1994;**30**:16–22.
46. Pawlowski V, Révillion F, Hebbar M, Hornez L, Peyrat J-P. Prognostic value of the type I growth factor receptors in a large series of human primary breast cancers quantified with a real-time reverse transcription-polymerase chain reaction assay. *Clin Cancer Res* 2000;**6**:4217–25.
47. Sassen A, Rochon J, Wild P, Hartmann A, Hofstaedter F, Schwarz S, et al. Cytogenetic analysis of HER1/EGFR, HER2, HER3 and HER4 in 278 breast cancer patients. *Breast Cancer Res* 2008;**10**:R2.
48. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1–4 family of receptor tyrosine kinases in breast cancer. *J Pathol* 2003;**200**:290–7.
49. Koutras AK, Kalogeras KT, Dimopoulos MA, Wirtz RM, Dafni U, Briasoulis E, et al. Evaluation of the prognostic and predictive value of HER family mRNA expression in high-risk early breast cancer: a Hellenic Cooperative Oncology Group (HeCOG) study. *Br J Cancer* 2008;**99**:1775–85.
50. Lee Y, Cho S, Seo JH, Shin BK, Kim HK, Kim I, et al. Correlated expression of erbB-3 with hormone receptor expression and favorable clinical outcome in invasive ductal carcinomas of the breast. *Am J Clin Pathol* 2007;**128**:1041–9.
51. Russnes HG, Lingjaerde OC, Borresen-Dale AL, Caldas C. Breast cancer molecular stratification: from intrinsic subtypes to integrative clusters. *Am J Pathol* 2017;**187**:2152–62.
52. Mujoo K, Choi BK, Huang Z, Zhang N, An Z. Regulation of ERBB3/HER3 signaling in cancer. *Oncotarget* 2014;**5**:10222–36.
53. Yu D, Hung MC. Overexpression of ErbB2 in cancer and ErbB2-targeting strategies. *Oncogene* 2000;**19**:6115–21.
54. Eccles SA. The epidermal growth factor receptor/Erb-B/HER family in normal and malignant breast biology. *Int J Dev Biol* 2011;**55**:685–96.
55. Jathal MK, Chen L, Mudryj M, Ghosh PM. Targeting ErbB3: the new RTK(id) on the prostate cancer block. *Immunol Endocr Metab Agents Med Chem* 2011;**11**:131–49.
56. Mills GB, Yarden Y. The rebirth of a phoenix: ovarian cancers are addicted to ErbB-3. *Cancer Cell* 2010;**17**:217–8.
57. Sheng Q, Liu X, Fleming E, Yuan K, Piao H, Chen J, et al. An activated ErbB3/NRG1 autocrine loop supports *in vivo* proliferation in ovarian cancer cells. *Cancer Cell* 2010;**17**:298–310.
58. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;**316**:1039–43.
59. Huang S, Li C, Armstrong EA, Peet CR, Saker J, Amler LC, et al. Dual targeting of EGFR and HER3 with MEHD7945A overcomes acquired resistance to EGFR inhibitors and radiation. *Cancer Res* 2013;**73**:824–33.
60. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer* 2009;**9**:463–75.
61. Bianco R, Shin I, Ritter CA, Yakes FM, Basso A, Rosen N, et al. Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. *Oncogene* 2003;**22**:2812–22.
62. Sergina NV, Rausch M, Wang D, Blair J, Hann B, Shokat KM, et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature* 2007;**445**:437–41.

63. She Q-B, Solit D, Basso A, Moasser MM. Resistance to gefitinib in PTEN-null HER-overexpressing tumor cells can be overcome through restoration of PTEN function or pharmacologic modulation of constitutive phosphatidylinositol 3′-kinase/Akt pathway signaling. *Clin Cancer Res* 2003;**9**:4340–6.
64. Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, et al. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Sci Transl Med* 2011;**3**:99ra86.
65. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;**316**:1039–43.
66. Wilson TR, Lee DY, Berry L, Shames DS, Settleman J. Neuregulin-1-mediated autocrine signaling underlies sensitivity to HER2 kinase inhibitors in a subset of human cancers. *Cancer Cell* 2011;**20**:158–72.
67. Huang X, Gao L, Wang S, McManaman JL, Thor AD, Yang X, et al. Heterotrimerization of the growth factor receptors erbB2, erbB3, and insulin-like growth factor-I receptor in breast cancer cells resistant to herceptin. *Cancer Res* 2010;**70**:1204–14.
68. Liu B, Ordonez-Ercan D, Fan Z, Edgerton SM, Yang X, Thor AD. Downregulation of erbB3 abrogates erbB2-mediated tamoxifen resistance in breast cancer cells. *Int J Cancer* 2007;**120**:1874–82.
69. Liu B, Ordonez-Ercan D, Fan Z, Huang X, Edgerton SM, Yang X, et al. Estrogenic promotion of ErbB2 tyrosine kinase activity in mammary tumor cells requires activation of ErbB3 signaling. *Mol Cancer Res* 2009;**7**:1882–92.
70. Wang S, Huang X, Lee CK, Liu B. Elevated expression of erbB3 confers paclitaxel resistance in erbB2-overexpressing breast cancer cells *via* upregulation of Survivin. *Oncogene* 2010;**29**:4225–36.
71. Lyu H, Yang XH, Edgerton SM, Thor AD, Wu X, He Z, et al. The erbB3- and IGF-1 receptor-initiated signaling pathways exhibit distinct effects on lapatinib sensitivity against trastuzumab-resistant breast cancer cells. *Oncotarget* 2016;**7**:2921–35.
72. Agus DB, Akita RW, Fox WD, Lewis GD, Higgins B, Pisacane PI, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002;**2**:127–37.
73. Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). [comment]. *J Natl Cancer Inst* 2001;**93**:1852–7.
74. Nahta R, Yuan LX, Zhang B, Kobayashi R, Esteva FJ. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Res* 2005;**65**:11118–28.
75. Spencer KS, Graus-Porta D, Leng J, Hynes NE, Klemke RL. ErbB2 is necessary for induction of carcinoma cell invasion by ErbB family receptor tyrosine kinases. *J Cell Biol* 2000;**148**:385–97.
76. Saunus JM, Quinn MC, Patch AM, Pearson JV, Bailey PJ, Nones K, et al. Integrated genomic and transcriptomic analysis of human brain metastases identifies alterations of potential clinical significance. *J Pathol* 2015;**237**:363–78.
77. Da Silva L, Simpson PT, Smart CE, Cocciardi S, Waddell N, Lane A, et al. HER3 and downstream pathways are involved in colonization of brain metastases from breast cancer. *Breast Cancer Res* 2010;**12**:R46.
78. Adam L, Vadlamudi R, Kondapaka SB, Chernoff J, Mendelsohn J, Kumar R. Heregulin regulates cytoskeletal reorganization and cell migration through the p21-activated kinase-1 *via* phosphatidylinositol-3 kinase. *J Biol Chem* 1998;**273**:28238–46.
79. Chausovsky A, Waterman H, Elbaum M, Yarden Y, Geiger B, Bershadsky A. Molecular requirements for the effect of neuregulin on cell spreading, motility and colony organization. *Oncogene* 2000;**19**:878–88.
80. Hinton DR, He S, Graf K, Yang D, Hsueh WA, Ryan SJ, et al. Mitogen-activated protein kinase activation mediates PDGF-directed migration of RPE cells. *Exp Cell Res* 1998;**239**:11–5.
81. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. *Cancer Metastas- Rev* 2003;**22**:337–58.
82. Tan M, Yao J, Yu D. Overexpression of the c-erbB-2 gene enhanced intrinsic metastasis potential in human breast cancer cells without increasing their transformation abilities. *Cancer Res* 1997;**57**:1199–1205.
83. Fukata M, Nakagawa M, Kaibuchi K. Roles of Rho-family GTPases in cell polarisation and directional migration. *Curr Opin Cell Biol* 2003;**15**:590–7.
84. Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfield MD. Cellular function of phosphoinositide 3-kinases: implications for development, immunity, homeostasis, and cancer. *Annu Rev Cell Dev Biol* 2001;**17**:615–75.
85. Merlot S, Firtel RA. Leading the way: directional sensing through phosphatidylinositol 3-kinase and other signaling pathways. *J Cell Sci* 2003;**116**:3471–8.
86. Reddy KB, Nabha SM, Atanaskova N. Role of MAP kinase in tumor progression and invasion. *Cancer Metastas- Rev* 2003;**22**:395–403.
87. Webb DJ, Donais K, Whitmore LA, Thomas SM, Turner CE, Parsons JT, et al. FAK–Src signalling through paxillin, ERK and MLCK regulates adhesion disassembly. *Nat Cell Biol* 2004;**6**:154–61.
88. Xia Y, Karin M. The control of cell motility and epithelial morphogenesis by Jun kinases. *Trends Cell Biol* 2004;**14**:94–101.
89. Xue C, Liang F, Mahmood R, Vuolo M, Wyckoff J, Qian H, et al. ErbB3-dependent motility and intravasation in breast cancer metastasis. *Cancer Res* 2006;**66**:1418–26.
90. Pradeep S, Kim SW, Wu SY, Nishimura M, Chaluvally-Raghavan P, Miyake T, et al. Hematogenous metastasis of ovarian cancer: rethinking mode of spread. *Cancer Cell* 2014;**26**:77–91.
91. Lyu H, Wang S, Huang J, Wang B, He Z, Liu B. Survivin-targeting miR-542-3p overcomes HER3 signaling-induced chemoresistance and enhances the antitumor activity of paclitaxel against HER2-overexpressing breast cancer. *Cancer Lett* 2018;**420**:97–108.
92. Gala K, Chandarlapaty S. Molecular pathways: her3 targeted therapy. *Clin Cancer Res* 2014;**20**:1410–6.
93. Schoeberl B, Faber AC, Li D, Liang MC, Crosby K. Onsum M, et al. An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. *Cancer Res* 2010;**70**:2485–94.
94. Schoeberl B, Pace EA, Fitzgerald JB, Harms BD, Xu L, Nie L, et al. Therapeutically targeting ErbB3: a key node in ligand-induced activation of the ErbB receptor-PI3K axis. *Sci Signal* 2009;**2**:ra31.
95. Jiang N, Saba NF, Chen ZG. Advances in Targeting HER3 as an anticancer therapy. *Chemother Res Pract* 2012;**2012**:817304.
96. Aurisicchio L, Marra E, Luberto L, Carlomosti F, De Vitis C, Noto A, et al. Novel anti-ErbB3 monoclonal antibodies show therapeutic efficacy in xenografted and spontaneous mouse tumors. *J Cell Physiol* 2012;**227**:3381–8.
97. Aurisicchio L, Marra E, Roscilli G, Mancini R, Ciliberto G. The promise of anti-ErbB3 monoclonals as new cancer therapeutics. *Oncotarget* 2012;**3**:744–58.
98. McDonagh CF, Huhalov A, Harms BD, Adams S, Paragas V, Oyama S, et al. Antitumor activity of a novel bispecific antibody that targets the ErbB2/ErbB3 oncogenic unit and inhibits heregulin-induced activation of ErbB3. *Mol Cancer Ther* 2012;**11**:582–93.
99. Foreman PK, Gore M, Kobel PA, Xu L, Yee H, Hannum C, et al. ErbB3 inhibitory surrobodies inhibit tumor cell proliferation *in vitro* and *in vivo*. *Mol Cancer Ther* 2012;**11**:1411–20.
100. Wang S, Huang J, Lyu H, Cai B, Yang X, Li F, et al. Therapeutic targeting of erbB3 with MM-121/SAR256212 enhances antitumor activity of paclitaxel against erbB2-overexpressing breast cancer. *Breast Cancer Res* 2013;**15**:R101.
101. Huang J, Wang S, Lyu H, Cai B, Yang X, Wang J, et al. The anti-erbB3 antibody MM-121/SAR256212 in combination with trastuzumab exerts potent antitumor activity against trastuzumab-resistant breast cancer cells. *Mol Cancer* 2013;**12**:134.
102. Liu JF, Ray-Coquard I, Selle F, Poveda AM, Cibula D, Hirte H, et al. Randomized phase II trial of seribantumab in combination with paclitaxel in patients with advanced platinum-resistant or -refractory ovarian cancer. *J Clin Oncol* 2016;**34**:4345–53.

103. Schoeberl B, Kudla A, Masson K, Kalra A, Curley M, Finn G, et al. Systems biology driving drug development: from design to the clinical testing of the anti-ErbB3 antibody seribantumab (MM-121). *NPJ Syst Biol Appl* 2017;**3**:16034.
104. Malm M, Frejd FY, Stahl S, Lofblom J. Targeting HER3 using mono- and bispecific antibodies or alternative scaffolds. *MAbs* 2016;**8**:1195–209.
105. Arnett SO, Teillaud J-L, Wurch T, Reichert JM, Dunlop DC, Huber M. IBC's Proceedings of the 21st Annual Antibody Engineering and 8th Annual Antibody Therapeutics International Conferences and 2010 Annual Meeting of The Antibody Society December 5–9, 2010, San Diego, CA USA. MAbs: Landes Bioscience, 2011:133–52.
106. Shimizu T, Yonesaka K, Hayashi H, Iwasa T, Haratani K, Yamada H, et al. Phase 1 study of new formulation of patritumab (U3-1287) Process 2, a fully human anti-HER3 monoclonal antibody in combination with erlotinib in Japanese patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2017;**79**:489–495.
107. Yonesaka K, Hirotani K, Kawakami H, Takeda M, Kaneda H, Sakai K, et al. Anti-HER3 monoclonal antibody patritumab sensitizes refractory non-small cell lung cancer to the epidermal growth factor receptor inhibitor erlotinib. *Oncogene* 2016;**35**:878–86.
108. Mirschberger C, Schiller CB, Schraml M, Dimoudis N, Friess T, Gerdes CA, et al. RG7116, a therapeutic antibody that binds the inactive HER3 receptor and is optimized for immune effector activation. *Cancer Res* 2013;**73**:5183–94.
109. Kawakami H, Yonesaka K. HER3 and its ligand, heregulin, as targets for cancer therapy. *Recent Pat Anticancer Drug Discov* 2016;**11**:267–274.
110. Meulendijks D, Jacob W, Martinez-Garcia M, Taus A, Lolkema MP, Voest EE, et al. First-in-human phase I study of lumretuzumab, a glycoengineered humanized anti-HER3 monoclonal antibody, in patients with metastatic or advanced HER3-positive solid tumors. *Clin Cancer Res* 2016;**22**:877–85.
111. Meulendijks D, Jacob W, Voest EE, Mau-Sorensen M, Martinez-Garcia M, Taus A, et al. Phase Ib study of lumretuzumab plus cetuximab or erlotinib in solid tumor patients and evaluation of HER3 and heregulin as potential biomarkers of clinical activity. *Clin Cancer Res* 2017;**23**:5406–15.
112. Schneeweiss A, Park-Simon TW, Albanell J, Lassen U, Cortes J, Dieras V, et al. Phase Ib study evaluating safety and clinical activity of the anti-HER3 antibody lumretuzumab combined with the anti-HER2 antibody pertuzumab and paclitaxel in HER3-positive, HER2-low metastatic breast cancer. *Invest New Drugs* 2018. Available from: <http://dx.doi.org/10.1007/s10637-018-0562-4>.
113. Sala G, Traini S, D'Egidio M, Vianale G, Rossi C, Piccolo E, et al. An ErbB-3 antibody, MP-RM-1, inhibits tumor growth by blocking ligand-dependent and independent activation of ErbB-3/Akt signaling. *Oncogene* 2012;**31**:1275–86.
114. Sala G, Rapposelli IG, Ghasemi R, Piccolo E, Traini S, Capone E, et al. EV20, a Novel Anti-ErbB-3 humanized antibody, promotes ErbB-3 down-regulation and inhibits tumor growth *in vivo*. *Transl Oncol* 2013;**6**:676–84.
115. Le Clorennec C, Bazin H, Dubreuil O, Larbouret C, Ogier C, Lazrek Y, et al. Neuregulin 1 allosterically enhances the antitumor effects of the noncompeting anti-HER3 antibody 9F7-F11 by increasing its binding to HER3. *Mol Cancer Ther* 2017;**16**:1312–23.