


REVIEW

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Development of Effective Therapeutics Targeting HER3 for Cancer Treatment

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Abstract

HER3 is the third member of the human epidermal growth factor receptor (HER/EGFR) family, and unlike its other family members, is unique due to its minimal intrinsic kinase activity. As a result, HER3 has to interact with another receptor tyrosine kinase (RTK), such as EGFR or HER2, in order to activate the PI-3 K/Akt, MEK/MAPK, Jak/Stat pathways, as well as Src kinase. Over-expression of HER3 in various human cancers promotes tumor progression by increasing metastatic potential and acting as a major cause of treatment failure. Effective inhibition of HER3, and/or the key downstream mediators of HER3 signaling, is thought to be required to overcome resistance and enhance therapeutic efficacy. To date, there is no known HER3-targeted therapy that is approved for breast cancer, with a number of anti-HER3 antibodies current in various stages of development and clinical testing. Recent data suggests that the epigenetic strategy of using a histone deacetylase (HDAC) inhibitor, or functional cooperative miRNAs, may be an effective way to abrogate HER3 signaling. Here, we summarize the latest advances in our understanding of the mechanism of HER3 signaling in tumor progression, with continuing research towards the identification of therapeutic anti-HER3 antibodies. We will also examine the potential to develop novel epigenetic approaches that specifically target the HER3 receptor, along with important key downstream mediators that are involved in cancer treatment.

Keywords: HER3, Cell signaling, Targeted therapy, Epigenetic approach, miRNA

Introduction

The human epidermal growth factor receptor (HER) family, including the epidermal growth factor receptor (EGFR, or HER1/*erbB1*), HER2 (or *erbB2/neu*), HER3 (or *erbB3*), and HER4 (*erbB4*) is arguably the most important receptor tyrosine kinase (RTK) family involved with normal cell development and tumorigenesis [1, 2]. Elevated expression of the HER family members is frequently observed in a wide variety of human cancers, including colorectal cancer, gastric cancer, breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, head and neck cancer, pancreatic cancer and cervical cancer, and has been shown to play a critical role in cancer development [3, 4]. Both EGFR and HER4 have several ligands, with HER3 exhibiting only a single ligand, called heregulin (HRG) or neuregulin (NRG). The HER2 receptor has no known ligand. When a ligand binds to

the extracellular region of EGFR, HER3, or HER4, it leads to a receptor-receptor interaction that results in dimerization [5], which is one of the key features of the HER receptors having the capacity for any two of the family members to form either homo- or hetero-dimers. Dimerization is the initial step critical for HER receptor function and activation of the downstream signaling, such as the PI-3 K/Akt, MEK/MAPK, Jak/Stat pathways, Src kinase, and several others [4, 6]. EGFR, HER3, and HER4 normally exist as molecularly folded monomers (inactive state) to prevent dimerization [7, 8]. In contrast, HER2 receptor always stays in a constitutively active conformation with its dimerization arm opening ready for interaction with another receptor [7].

Unlike other HER family members (EGFR, HER2, and HER4), the HER3 receptor has little or no tyrosine kinase activity [9, 10]. It has been shown that HER3 frequently co-expresses, and interacts with, another RTK to form a heterodimeric complex, which subsequently activates oncogenic signaling. This is especially true for the PI-3 K/Akt pathway and Src kinase to increase cancer

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cell survival and proliferation [11–13]. Studies on the underlying mechanisms demonstrate that HER3 signaling promotes cancer progression mainly through influencing two aspects of cancer biology, mainly by enhancing metastatic potential of tumor cells and causing treatment failures in cancer therapy [14–16]. There is accumulating data that strongly support the notion that developing effective HER3-targeted therapy is required to overcome resistance, enhance treatment efficacy and increase survival rates of cancer patients. Due to the lack of, or weak, kinase activity [9, 10], targeting HER3 with a blocking antibody (Ab) is the only strategy currently being examined in pre-clinical studies and clinical evaluation in cancer patients [17–21]. Recent studies offer new hopes to develop epigenetic approaches, such as using a histone deacetylase inhibitor (HDACi) [22, 23] specific miRNAs [24–26], or by targeting HER3 and its key downstream mediators.

HER3 Promotion of Tumor Metastasis and Function as a Major Determinant of Cancer Drug Sensitivity

Elevated expression of HER3 is frequently observed in a variety of human cancers, with its over-expression of HER3 associated with poor clinical outcomes [12, 27–32]. HER3 must interact with another receptor to transduce cell signaling, often partnering with HER2 to exhibit its oncogenic activity in tumors with HER2 over-expression [12, 33–35]. A recent report further demonstrates that over-expression of HER3 is associated with a poorer survival rate in patients with cancers, including colorectal cancer, gastric cancer, breast cancer, melanoma, ovarian cancer, head and neck cancer, pancreatic cancer and cervical cancer [36]. Moreover, it showed that the impact of HER3 on clinical outcomes is much more prevalent in the tumors simultaneously over-expressing HER2 [36]. This suggested that it is the HER2/HER3 heterodimer that plays a crucial role in cancer progression. Others have shown that enhanced HER3 signaling facilitates tumor cell motility and intravasation in metastatic breast cancer to the lung [37]. It was identified that a HER3-lncRNA (long non-coding RNA) axis regulates bone metastasis in breast cancer [38, 39].

In addition, the HER3 ligand, HRG, can stimulate chemotaxis and invasion via HER2/HER3 heterodimers [40]. It has been reported that HRG-induced activation of HER3 signaling is important in breast cancer brain metastasis [41, 42]. In addition to brain metastases derived from a primary breast cancer, which can overexpress HER3 [42, 43], increased HRG production by the stromal cells within the brain microenvironment may also result in activation of HER3 and its downstream signaling, thereby promoting breast cancer brain metastasis [41, 42, 44]. Activation of the PI-3K/Akt and MEK/MAPK signaling, two major downstream pathways of

HER3 signaling, can be critical for cell motility and chemotaxis [40, 45–49]. The PI-3K pathway is able to regulate cytoskeleton and cancer cell survival through Rho family G proteins and Akt activation, respectively [50–52]. The MAPK's control cell proliferation, adhesion, and gene expression essential for motility and invasion [53–55]. It is possible that HER3-dependent motility contributes to cancer metastasis independent of its effects on tumor growth [37]. A recent study challenges our current view on tumor metastasis of ovarian cancer. While local spread to the omentum was thought to be the main mechanism of ovarian cancer metastasis, it 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. In fact, HRG-induced HER3 signaling appears to be the dominant pathway involved with the hematogenous metastasis of ovarian cancer [56].

Interestingly, non-coding RNA (ncRNA), such as the long ncRNA (lncRNA) *MAYA* has also been shown to play an important role in HER3-mediated tumor metastasis [39]. Upon HRG stimulation, the RTK-like orphan receptor ROR1 phosphorylates HER3. The phosphorylated HER3 then recruits a *MAYA*-containing RNA-protein complex to methylate Hippo/MST1. This methylation further leads to MST1 inactivation and activation of YAP target genes in breast cancer cells, thereby inducing osteoclast differentiation and bone metastasis [38]. Thus, the ROR1-HER3-lncRNA (*MAYA*) axis represents a novel mechanism regulating the Hippo-YAP pathway to control bone metastasis in breast cancer [38, 39]. In the last several years, our laboratory has strived to identify key downstream mediators of HER3 signaling in metastatic breast cancer. Two tumor suppressive miRNAs, miR-203 and miR-542-3p were found to be specifically down-regulated by HER3 signaling in HER2-over-expressing breast cancer cells [25]. Further analyses reveal that both miR-203 and miR-542-3p target a cohort of genes, including *Survivin*, *ZEB1*, *ZEB2*, and *Snail1*, responsible for drug resistance, epithelial-mesenchymal transition (EMT) and tumor metastasis (Liu lab unpublished data). Our data suggest that HER3 signaling may promote cancer metastasis via modulating expression of specific miRNAs. We believe that such studies in this innovative area will provide a new avenue for the identification of novel therapeutic approaches to abrogate HER3-mediated cancer metastasis.

Numerous studies implicate HER3 activation as a major cause of treatment failure in cancer therapy [15]. HER3 signaling plays a crucial role in the development of human cancers that exhibit a drug resistance phenotype, including HER2-over-expressing breast cancer [11, 12], castration-resistant prostate cancer [57],

platinum-resistant/refractory ovarian cancer [58, 59], and EGFR tyrosine kinase inhibitor (TKI)-resistant non-small cell lung cancer (NSCLC) [60, 61]. It is now clear that the compensatory up-regulation of HER3 along with the sustained PI-3 K/Akt signaling is an important mechanism resulting in resistance to EGFR-targeted therapy, gefitinib [1, 62–64]. In addition, elevated expression of HRG has been shown to be a possible mechanism of resistance to the anti-EGFR Ab, cetuximab, in patients with colorectal cancer [65]. For squamous cell carcinoma of the head and neck, cell lines sensitive to the dual EGFR/HER2 inhibitor, lapatinib, increased HRG and strongly activated HER3 which 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. Our laboratory has been focusing on understanding the biologic function of HER3 as it relates to the progression of HER2-over-expressing breast cancer. We also show that elevated expression of HER3 in HER2-over-expressing 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 in breast cancer [13, 16]. One interesting observation arises from our studies on the underlying mechanism of HER3-mediated resistance to trastuzumab (or Herceptin). While both HER3 and the insulin-like growth factor-I receptor (IGF-1R)-mediated signaling have been reported to contribute to trastuzumab resistance [72–74], the relationship between HER3 and IGF-1R in trastuzumab resistance was not previously appreciated.

We found that HER2 interacted with both HER3 and IGF-1R, forming a heterotrimeric complex in trastuzumab-resistant breast cancer cells. In fact, it was the heterotrimer of HER2/HER3/IGF-1R that played a causal role leading to trastuzumab resistance [67]. Further studies revealed that HER3 and IGF-1R triggered different signaling pathways contributing to trastuzumab resistance, with HER3 activating both PI-3 K/Akt signaling and Src kinase, whereas IGF-1R mainly influenced Src activation [67]. Interestingly, our recent data shows that HER3 and IGF-1R exhibit distinct effects upon the sensitivity of HER2-over-expressing breast cancer cells to lapatinib [71]. While HER3 signaling also induces lapatinib resistance in the trastuzumab-resistant breast cancer cells, IGF-1R signaling did not alter lapatinib sensitivity [71]. Our studies on the molecular mechanism of HER3-mediated resistance to chemotherapy paclitaxel showed that survivin, up-regulated by HER3, served as a

key downstream mediator in HER3 signaling-induced paclitaxel resistance [70].

Therapeutic Antibodies against HER3 in Clinical and Pre-Clinical Investigations

The elevated expression of HER3 promotes cancer progression and correlates with a worse survival rate in patients with cancers of colon, gastric, breast, lung, ovarian, melanoma, head and neck, pancreatic and cervical [15, 36, 75], emphasizing the importance of developing effective therapeutics that specifically target and inhibit the HER3 receptor [16, 76, 77]. It is believed that inactivation of HER3, as well as its downstream signaling, is required to overcome this resistance and effectively treat cancer patients. Due to the intrinsic low kinase activity [9, 10], targeting HER3 with a blocking Ab has been the only strategy examined in pre-clinical studies [78, 79] and for patients with advanced solid tumors (<http://www.clinicaltrials.gov>). Advances have been made to identify HER3-targeted therapy [17, 80, 81], and a number of anti-HER3 Abs exhibit anti-tumor activity in vivo and show promise as novel cancer therapeutics [18, 82, 83]. In addition to developing monoclonal Abs directly against HER3, recent studies have also identified bi-specific Abs that are dual targets for EGFR/HER3 [61] or HER2/HER3 [84]. These exert potent anti-tumor activities in both laboratory studies and clinic investigations [80]. As this review focuses on human cancers, Table 1 only lists the current clinical trials in cancer patients to test the therapeutic activity of several anti-HER3 monoclonal and bi-specific Abs.

The development of 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 humanized, anti-HER3 monoclonal Ab that is currently being examined in several clinical trials in patients with advanced solid tumors [18], including a phase III trial in patients with NSCLC [85]. This Ab was able to inhibit proximal and distal HER signaling and induce rapid internalization of HER3 [86]. The Ab, patritumab, inhibited cell proliferation in various cancer cell lines (breast, lung, colorectal) that are resistant to other HER inhibitors [86]. It dramatically reduced colony formation of pancreatic cancer cells and inhibited tumor growth in tumor xenograft models of pancreatic cancer, NSCLC and colorectal cancer [57]. Patritumab has been shown to overcome HRG-dependent resistance to EGFR inhibitors in NSCLC in vitro and in vivo. Such data further supports the interest in ongoing clinical trials testing patritumab in combination with EGFR TKIs, such as erlotinib, to treat NSCLC patients with high expression of HRG [85, 87, 88].

Table 1 Mono- and bi-specific anti-HER3 Abs under clinical studies in cancer patients

Abs	Target	Most advanced clinical phase	Clinicaltrials.gov identifier	Current Results on clinicaltrials.gov	Sponsor
mAbs:					
U3-1287/Patritumab	HER3	Phase III	NCT02134015	Terminated (Pre-defined criteria Not reached)	Daiichi Sankyo
MM-121/Seribantumab	HER3	Phase II	NCT00994123	MM-121+ erlotinib ineffective to prolong PFS in EGFR WT NSCLC	Merrimack Pharmaceuticals
RG7116/Lumretuzumab	HER3	Phase I	NCT01482377	No results posted	Roche
LJM716/Elgemtumab	HER3	Phase I/II	NCT01822613	No results posted	Novartis
U3-1402	HER3	Phase I/II	NCT02980341	Ongoing	Daiichi Sankyo
AV-203	HER3	Phase I	NCT01603979	No results posted	Aveo Oncology
KTN3379/CDX-3379	HER3	Phase I	NCT02014909	No results posted	Celldex Therapeutics
GSK2849330	HER3	Phase I	NCT01966445	Results submitted, But not posted	GlaxoSmithKline
Bispecific Abs:					
MM-111	HER2/HER3	Phase II	NCT01774851	Terminated (Lack of efficacy)	Merrimack Pharmaceuticals
MCLA-128	HER2/HER3	Phase II	NCT03321981	Ongoing	Merus NV
MM-141/Istiratutumab	HER3/IGF-1R	Phase II	NCT02399137	No results posted	Merrimack Pharmaceuticals
MEHD7945A/Duligotumab	HER3/EGFR	Phase II	NCT01652482	No results posted	Genentech

The monoclonal Ab, MM-121/seribantumab (Merrimack Pharmaceuticals, Cambridge, MA), is a human, anti-HER3 monoclonal IgG2 Ab. It blocks ligand-induced HER2/HER3 dimerization and inhibits downstream signaling. MM-121 exerts potent anti-tumor activity in pre-clinical studies of various human cancers [78, 79]. We have shown that MM-121 was able to abrogate HER3 signaling-mediated resistance to trastuzumab and paclitaxel in HER2-over-expressing breast cancer cells via the inactivation of HER3 and its downstream PI-3 K/Akt signaling [89, 90]. Our data may facilitate the development of clinical trials to test the efficacy of MM-121 in combination with trastuzumab or paclitaxel in HER2-overexpressing breast cancer patients who have developed resistance to trastuzumab or paclitaxel.

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-low breast cancer and EGFR wild-type NSCLC [91, 92]. Lumretuzumab/RG7116 (Roche Diagnostics GmbH, Penzberg, Germany) is a humanized anti-HER3 IgG1 monoclonal Ab. It binds to the extracellular domain of HER3 with high affinity to prevent HRG binding [93]. As a glyco-engineered Ab, lumretuzumab has an enhanced antibody-dependent

cell-mediated cytotoxicity (ADCC) activity when compared with the non-glyco-engineered parental antibody [17]. Although lumretuzumab was well tolerated and showed evidence of clinical activity in a phase I trial [19], two recent phase Ib studies suggest otherwise. The toxicity profile of lumretuzumab in combination with the EGFR-targeted therapies, cetuximab and erlotinib, was manageable, but it exerted only a minimal clinical benefit in various cancers [20]. 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 [21]. MM-111 (Merrimack Pharmaceuticals, Cambridge, MA) is a bi-specific Ab, dual-targeting HER2/HER3, inhibiting the PI-3 K/Akt signaling [84]. The safety and clinical activity of MM-111 is now being tested in several phase I/II clinical trials of cancer patients [81, 85].

It is worth mentioning that the anti-HER3 Ab (MP-RM-1), and its humanized version, (EV20) exhibit potent anti-tumor effects in several cancer types in vitro and in vivo [94, 95]. Although EV20 is only being examined in the pre-clinical setting, its capacity to inhibit both ligand-dependent and independent activation of HER3 [94, 95] yields a high level of enthusiasm that EV20 may have a broader effect on blocking HER3 signaling compared with other similar Abs (like MM-121) that only block ligand-induced HER3 activation. In

addition to developing specific Abs directly against HER3, recent studies have attempted to identify Ab-like agent(s) targeting HER3. The HER3 inhibitors are based upon a novel biologic scaffold, termed surrobody, that has been developed, showing significant anti-proliferative effects on cancer cells in vitro and in vivo [96].

An HER1–3-neutralizing Ab mixture exerts a high anti-tumor activity against drug-resistant HER2-overexpressing breast cancers, suggesting that the multi-targeted Ab mixture represents a novel approach for effective treatment of breast cancers with HER2-overexpressing tumors [97]. Interestingly, an adenovirus encoding the full length human HER3 (Ad-HER3) receptor was generated to be utilized as a putative cancer “vaccine” [98]. Ad-HER3 not only induced potent T-cell anti-tumor responses, the HER3, vaccine-induced antibodies (HER3-VIAs) also provided additional activity to eliminate tumors in which HER3 signaling mediates aggressive behavior or acquired resistance to HER2-targeted therapy and triple-negative breast cancers [98]. Thus, clinical studies of vaccination against HER3 in combination with other therapies, such as trastuzumab to treat the refractory HER2-overexpressing breast cancers or chemotherapy like paclitaxel against triple-negative breast cancers may show a plausible therapeutic efficacy.

Emerging Strategy Targeting of HER3 Signaling with Therapeutic Potential

There has been a lot of research effort put forth to identify novel therapeutics and approaches which can

effectively inhibit HER3, or key downstream mediators of HER3 signaling. To this end, we discovered that the class I HDACi, entinostat, was able to potently down-regulate HER3 in HER2-over-expressing breast cancer cells [22]. Further studies revealed that entinostat induced expression of miR-125a, miR-125b, and miR-205, all of which were reported to directly target the 3’UTR of *erbB3* mRNA [99, 100]. The three miRNAs acted in concert to inhibit HER3 protein translation in HER2-over-expressing breast cancer cells [101]. Such exciting data support a novel hypothesis that effective targeting of HER3 may be achieved with the treatment of entinostat, or with functional cooperation from miR-125a, miR-125b, and miR-205 (Fig. 1).

Thus, we examined this idea with miR-125a and miR-205 in order to determine whether co-expression of the two miRNAs would exert functional cooperation to inhibit *erbB3* expression in HER2-over-expressing breast cancer cells. Our data showed that the miRNA (miR-125a/miR-205) cluster (co-expression of miR-125a and miR-205) was more effective than either miRNA alone to down-regulate HER3 in HER2-over-expressing breast cancer cells [24]. Importantly, we discovered that the miRNA (miR-125a/miR-205) cluster not only profoundly inhibited cell proliferation, but also significantly enhance trastuzumab- and paclitaxel-mediated anti-proliferative/anti-survival effects on HER2-over-expressing breast cancer cells [24]. Our data strongly support the notion that the miR-125a/miR-205 cluster may be developed as a novel, effective HER3-targeted therapy to enhance therapeutic efficacy against HER2-over-expressing breast cancer.

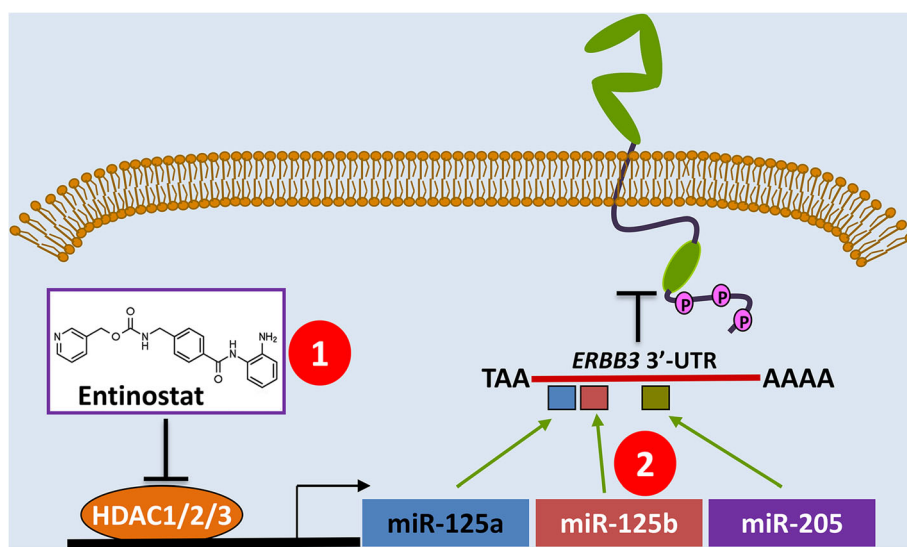


Fig. 1 A diagram showing the novel epigenetic approaches inhibiting HER3 for cancer treatment. The class I HDACi entinostat potently downregulates HER3 expression via induction of miR-125a, miR-125b, and miR-205, which act in concert to inhibit HER3 protein translation. Thus, the epigenetic strategy takes advantage of a novel mechanism of action (distinct from that of an anti-HER3 Ab) to abrogate HER3 signaling

Identification of the crucial downstream mediator(s) that relay(s) HER3 signaling-induced resistance shall facilitate the development of novel approaches to inhibit HER3 signaling and thereby enhance therapeutic efficacy for cancer treatment. Our previous studies found that elevated expression of HER3 conferred paclitaxel resistance in HER2-over-expressing breast cancer cells via up-regulation of survivin [70]. Although survivin has long been considered as a good molecular target for cancer treatment [102, 103], there has been no survivin-targeted therapy to date, with currently available strategies lacking both specificity and effectiveness [104]. We have recently shown that miR-203 and miR-542-3p play an essential role in HER3/PI-3 K/Akt signaling-mediated up-regulation of survivin [25]. These data provided an opportunity to examine miRNA-based therapeutic strategy inhibiting survivin to overcome HER3-mediated paclitaxel resistance. In order to define whether miR-203 and miR-542-3p may be useful for survivin-targeted therapeutics, we first performed bioinformatics analyses and found that miR-542-3p has three binding sites on the 3'-UTR of survivin mRNA, whereas miR-203 has only one binding site [105].

This interesting observation inspired us to test the hypothesis that the miRNAs with multiple binding sites on the 3'-UTR of survivin mRNA shall be more effective than those with a single binding site in the down-regulation of survivin. Both in vitro and in vivo experiments revealed that introduction of miR-542-3p mimic not only exhibited a more potent activity to specifically down-regulate survivin, but also markedly enhanced paclitaxel-mediated anti-tumor effects via inhibition of proliferation and induction of apoptosis [25]. These data suggest that miR-542-3p-replacement therapy holds potential for further development as a novel strategy for surviving inhibition, thereby overcoming HER3 signaling-induced paclitaxel resistance.

Moreover, our study further support the idea that functional cooperation exists among the multiple binding sites of one miRNA, which is in agreement with our recent report showing that the miR-125a/miR-205 cluster potently inhibits HER3 expression in HER2-over-expressing breast cancer cells [24]. It is likely that the multiple binding sites of one miRNA and the "sister" miRNAs, which have common targets [26], act synergistically to repress the target, suggesting that the miRNAs with multiple binding sites may be more promising in miRNA-replacement therapy. Thus, a novel epigenetic strategy has emerged to target HER3 and/or its key downstream mediator to abrogate HER3-mediated treatment failure in cancer therapy. The HDACi entinostat or the miR-125a/miR-205 cluster inhibit HER3 expression and miR-542-3p may act as an effective survivin-targeted therapy, all of which will overcome

HER3 signaling-mediated resistance and thereby enhance therapeutic efficacy against HER2-overexpressing breast cancer. Due to the novel epigenetic approach that aims to reduce HER3 or survivin protein levels, not just inhibits HER3 signaling, it has great potential to eliminate the chance for tumor cells to develop resistance after an initial response to standard therapy.

Future Development

Clearly, a therapy that can effectively inhibit HER3 signaling is required to overcome drug resistance, enhance therapeutic efficacy and increase survival of cancer patients. While several anti-HER3 Abs with therapeutic potential are actively under clinical evaluations, the hope is high for a select few, mainly MM-121/seribantumab and patritumab, both of which have shown encouraging clinic benefits in patients with non-small cell lung cancer [88, 92]. In addition, the US FDA has recently (10/30/2017) granted an orphan drug designation to MM-121 for the treatment of HRG-positive NSCLC (<http://investors.merrimack.com/node/11346>). Prior to its final approval, one of the obstacles may have to attribute to the unique biologic feature of the HER3 receptor. As we know, HER3 has to interact with, and usually acts as a co-receptor for, another RTK, with HER2 being the most important one [106]. Thus, therapeutic targeting of HER3 alone may not show dramatic anti-tumor effects. It needs to combine with other treatment(s). The challenges are directed towards a HER3-targeted therapy combined with a second effective therapy, and how to combine a HER3-targeted therapy with other therapeutics. Lastly, it is a relevant question to ask when to combine a HER3-targeted therapy together with another agent. Further investigations on these questions should provide valuable data to facilitate the FDA approval for the anti-HER3 Abs currently under clinical testing.

The emerging epigenetic approaches targeting HER3 and/or its signaling are theoretically based upon RNA interference (RNAi) technology-based therapy, such as "small interfering RNA" (siRNA)- or miRNA-replacement therapy, which is actively being explored as a new strategy to treat human diseases, including cancer [107]. The regulatory potential of miRNAs on the entire signaling networks within the cells, and involvement in cancer development and progression, has resulted in the miRNAs as promising molecular targets for cancer treatment [108–111]. Recent studies in this area have driven the future development of miRNAs as cancer therapeutics, moving very quickly from the bench to clinic application [107, 112, 113]. Unfortunately, the first clinical trial using miR-34 mimics (trade name: MRX34, Mirna Therapeutics, Austin, TX) as a replacement therapy, failed due to multiple immune-related side effects. It was hoped that further analysis of its full

pre-clinical and clinical data would provide useful information on the future development of MRX34 as a cancer therapeutics (<https://www.bizjournals.com/austin/news/2016/09/21/austin-drug-company-halts-clinical-studies-after.html>). In our effort to identify novel therapeutic approach targeting HER3, we find that the miR-125a/miR-205 cluster potently inhibits HER3 expression [24], and miR-542-3p, because of its three binding sites on the 3'UTR of survivin mRNA, and holds great potential as an effective survivin-targeted therapy [25]. Our data strongly suggest that in the future, functional cooperative miRNAs or the miRNAs with multiple binding sites on a target may be more promising candidates for the development of miRNA-replacement therapy. A few months ago (8/10/2018), the US FDA approved the first-ever, siRNA product as an Orphan Drug Designation (Onpattro or patisiran) to treat the rare hereditary disease transthyretin-mediated amyloidosis in adult patients (<https://www.biologicsblog.com/fda-approves-first-ever-sirna-therapy>). This approval marks a significant milestone in the story of RNAi technology and clearing the way for a new type of therapeutic strategy. We believe that the novel epigenetic approaches, using a specific HDACi (entonostat) or miRNA-replacement therapy, targeting HER3 and/or its key downstream mediator deserves further investigation for cancer treatment.

Abbreviations

Ab: Antibody; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; FDA: Food and Drug Administration; HDAC: Histone deacetylase; HDACi: HDAC inhibitor; 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; PI-3 K: Phosphoinositide 3-kinase; RTK: Receptor tyrosine kinase; TKI: Tyrosine kinase inhibitor

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Authors' Contributions

The authors' contributions to this work are reflected in the order shown, with the exception of BL who finalized the manuscript. XL, SL, HL, and BL performed the literature search, table completion and model drawing. XL, AIR, and BL drafted and edited the manuscript. AIR, YZ, and BL conceived of the review and participated in its design and coordination. All authors read and approved the final manuscript.

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Consent for Publication

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References

- Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer*. 2009;9:463–75.
- Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol*. 2009;21:177–84.
- 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.
- Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J*. 2000;19:3159–67.
- Ogiso H, Ishitani R, Nureki O, Fukai S, Yamanaka M, Kim J-H, Saito K, Sakamoto A, Inoue M, Shirouzu M. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. *Cell*. 2002;110:775–87.
- 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.
- Burgess AW, Cho H-S, Eigenbrot C, Ferguson KM, Garrett TP, Leahy DJ, Lemmon MA, Sliwkowski MX, Ward CW, Yokoyama S. An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors. *Mol Cell*. 2003;12:541–52.
- Cho H-S, Leahy DJ. Structure of the extracellular region of HER3 reveals an interdomain tether. *Science*. 2002;297:1330–3.
- 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.
- 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.
- Holbro T, Beerli RR, Maurer F, Koziczak M, Barbas CF 3rd, 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.
- Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoeflich KP, Sliwkowski MX, Stern HM. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68:5878–87.
- 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.
- Lyu H, Han A, Polsdofer E, Liu S, Liu B. Understanding the biology of HER3 receptor as a therapeutic target in human cancer. *Acta Pharm Sin B*. 2018;8:503–10.
- 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.
- Ma J, Lyu H, Huang J, Liu B. Targeting of erbB3 receptor to overcome resistance in cancer treatment. *Mol Cancer*. 2014;13:105.
- Kawakami H, Yonesaka K. HER3 and its ligand, Heregulin, as targets for Cancer therapy. *Recent Pat Anticancer Drug Discov*. 2016;11:267–74.
- Malm M, Frejd FY, Stahl S, Lofblom J. Targeting HER3 using mono- and bispecific antibodies or alternative scaffolds. *MAbs*. 2016;8:1195–209.
- Meulendijks D, Jacob W, Martinez-Garcia M, Taus A, Lolkema MP, Voest EE, Langenberg MH, Fleitas Kanonnikoff T, Cervantes A, De Jonge MJ, Sleijfer S, Soerensen MM, Thomas M, Ceppi M, Meneses-Lorente G, James I, Adessi C, Michielin F, Abiraj K, Bossenmaier B, Schellens JH, Weisser M, Lassen UN. 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.
20. Meulendijks D, Jacob W, Voest EE, Mau-Sorensen M, Martinez-Garcia M, Taus A, Fleitas T, Cervantes A, Lolkema MP, Langenberg MHG, De Jonge MJ, Sleijfer S, Han JY, Calles A, Felipe E, Kim SW, Schellens JHM, Wilson S, Thomas M, Ceppi M, Meneses-Lorente G, James I, Vega-Harrington S, Dua R, Nguyen M, Steiner L, Adessi C, Michielin F, Bossenmaier B, Weisser M, Lassen UN. 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.
 21. Schneeweiss A, Park-Simon TW, Albanell J, Lassen U, Cortes J, Dieras V, May M, Schindler C, Marme F, Cejalvo JM, Martinez-Garcia M, Gonzalez I, Lopez-Martin J, Welt A, Levy C, Joly F, Michielin F, Jacob W, Adessi C, Moisan A, Meneses-Lorente G, Racek T, James I, Ceppi M, Hasmann M, Weisser M, Cervantes A. 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;36:848–59.
 22. Huang X, Gao L, Wang S, Lee CK, Ordentlich P, Liu B. HDAC inhibitor SNDX-275 induces apoptosis in erbB2-overexpressing breast cancer cells via down-regulation of erbB3 expression. *Cancer Res.* 2009;69:8403–11.
 23. Huang X, Wang S, Lee CK, Yang X, Liu B. HDAC inhibitor SNDX-275 enhances efficacy of trastuzumab in erbB2-overexpressing breast cancer cells and exhibits potential to overcome trastuzumab resistance. *Cancer Lett.* 2011;307:72–9.
 24. Lyu H, Huang J, He Z, Liu B. Targeting of HER3 with functional cooperative miRNAs enhances therapeutic activity in HER2-overexpressing breast cancer cells. *Biol Proced Online.* 2018;20:16.
 25. 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.
 26. Wahdan-Alaswad R, Liu B. "Sister" miRNAs in cancers. *Cell Cycle.* 2013;12:3703–4.
 27. 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.
 28. Maurer CA, Friess H, Kretschmann B, Zimmermann A, Stauffer A, Baer HU, Korc M, Buchler MW. Increased expression of erbB3 in colorectal cancer is associated with concomitant increase in the level of erbB2. *Hum Pathol.* 1998;29:771–7.
 29. Naidu R, Yadav M, Nair S, Kutty MK. Expression of c-erbB3 protein in primary breast carcinomas. *Br J Cancer.* 1998;78:1385–90.
 30. Sassen A, Rochon J, Wild P, Hartmann A, Hofstaedter F, Schwarz S, Brockhoff G. Cytogenetic analysis of HER1/EGFR, HER2, HER3 and HER4 in 278 breast cancer patients. *Breast Cancer Res.* 2008;10:R2.
 31. Travis A, Pinder SE, Robertson JF, Bell JA, Wencyk P, Gullick WJ, Nicholson RI, Poller DN, Blamey RW, Elston CW, Ellis IO. C-erbB-3 in human breast carcinoma: expression and relation to prognosis and established prognostic indicators. *Br J Cancer.* 1996;74:229–33.
 32. 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.
 33. Alimandi M, Romano A, Curia MC, Muraro R, Fedi P, Aaronson SA, Di Fiore PP, Kraus MH. Cooperative signaling of ErbB3 and ErbB2 in neoplastic transformation and human mammary carcinomas. *Oncogene.* 1995;10:1813–21.
 34. 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.
 35. 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.
 36. 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.
 37. Xue C, Liang F, Mahmood R, Vuolo M, Wyckoff J, Qian H, Tsai K-L, Kim M, Locker J, Zhang Z-Y, Segall JE. ErbB3-dependent motility and intravasation in breast cancer metastasis. *Cancer Res.* 2006;66:1418–26.
 38. Li C, Wang S, Xing Z, Lin A, Liang K, Song J, Hu Q, Yao J, Chen Z, Park PK, Hawke DH, Zhou J, Zhou Y, Zhang S, Liang H, Hung MC, Gallick GE, Han L, Lin C, Yang L. A ROR1-HER3-lncRNA signalling axis modulates the hippo-YAP pathway to regulate bone metastasis. *Nat Cell Biol.* 2017;19:106–19.
 39. Zhuo W, Kang Y. Lnc-ing ROR1-HER3 and hippo signalling in metastasis. *Nat Cell Biol.* 2017;19:81–3.
 40. 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.
 41. 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.
 42. Kodack DP, Askoxylakis V, Ferraro GB, Sheng Q, Badeaux M, Goel S, Qi X, Shankaraiah R, Cao ZA, Ramjiawan RR, Bezwada D, Patel B, Song Y, Costa C, Naxerova K, Wong CSF, Kloepper J, Das R, Tam A, Tanboon J, Duda DG, Miller CR, Siegel MB, Anders CK, Sanders M, Estrada MV, Schlegel R, Arteaga CL, Brachtel E, Huang A, Fukumura D, Engelman JA, Jain RK. The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation. *Sci Transl Med.* 2017;9(391):eaal4682.
 43. Saunus JM, Quinn MC, Patch AM, Pearson JV, Bailey PJ, Nones K, McCart Reed AE, Miller D, Wilson PJ, Al-Ejeh F, Mariasegaram M, Lau Q, Withers T, Jeffrey RL, Reid LE, Da Silva L, Matsika A, Niland CM, Cummings MC, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Anderson MJ, Fink JL, Holmes O, Kazakoff S, Leonard C, Newell F, Taylor D, Waddell N, Wood S, Xu Q, Kassahn KS, Narayanan V, Taib NA, Teo SH, Chow YP, kConFab, Jat PS, Brandner S, Flanagan AM, Khanna KK, Chenevix-Trench G, Grimmond SM, Simpson PT, Waddell N, Lakhani SR. Integrated genomic and transcriptomic analysis of human brain metastases identifies alterations of potential clinical significance. *J Pathol.* 2015;237:363–78.
 44. Da Silva L, Simpson PT, Smart CE, Cocciardi S, Waddell N, Lane A, Morrison BJ, Vargas AC, Healey S, Beesley J, Pakkiri P, Parry S, Kurniawan N, Reid L, Keith P, Faria P, Pereira E, Skalova A, Bilous M, Balleine RL, Do H, Dobrovic A, Fox S, Franco M, Reynolds B, Khanna KK, Cummings M, Chenevix-Trench G, Lakhani SR. HER3 and downstream pathways are involved in colonization of brain metastases from breast cancer. *Breast Cancer Res.* 2010;12:R46.
 45. 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.
 46. 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.
 47. Hinton DR, He S, Graf K, Yang D, Hsueh WA, Ryan SJ, Law RE. Mitogen-activated protein kinase activation mediates PDGF-directed migration of RPE cells. *Exp Cell Res.* 1998;239:11–5.
 48. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. *Cancer Metastasis Rev.* 2003;22:337–58.
 49. 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;57:1199–205.
 50. 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.
 51. 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.
 52. Merlot S, Firtel RA. Leading the way: directional sensing through phosphatidylinositol 3-kinase and other signaling pathways. *J Cell Sci.* 2003;116:3471–8.
 53. Reddy KB, Nabha SM, Atanaskova N. Role of MAP kinase in tumor progression and invasion. *Cancer Metastasis Rev.* 2003;22:395–403.
 54. Webb DJ, Donais K, Whitmore LA, Thomas SM, Turner CE, Parsons JT, Horwitz AF. FAK-Src signalling through paxillin, ERK and MLCK regulates adhesion disassembly. *Nat Cell Biol.* 2004;6:154–61.
 55. Xia Y, Karin M. The control of cell motility and epithelial morphogenesis by Jun kinases. *Trends Cell Biol.* 2004;14:94–101.
 56. Pradeep S, Kim SW, Wu SY, Nishimura M, Chaluvally-Raghavan P, Miyake T, Pecot CV, Kim SJ, Choi HJ, Bischoff FZ, Mayer JA, Huang L, Nick AM, Hall CS, Rodriguez-Aguayo C, Zand B, Dalton HJ, Arumugam T, Lee HJ, Han HD, Cho MS, Rupaimoole R, Mangala LS, Sehgal V, Oh SC, Liu J, Lee JS, Coleman RL, Ram P, Lopez-Berestein G, Fidler IJ, Sood AK. Hematogenous metastasis of ovarian cancer: rethinking mode of spread. *Cancer Cell.* 2014;26:77–91.
 57. 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.

58. Mills GB, Yarden Y. The rebirth of a phoenix: ovarian cancers are addicted to ErbB-3. *Cancer Cell*. 2010;17:217–8.
59. Sheng Q, Liu X, Fleming E, Yuan K, Piao H, Chen J, Moustafa Z, Thomas RK, Greulich H, Schinzel A, Zaghul S, Batt D, Ettenberg S, Meyerson M, Schoeberl B, Kung AL, Hahn WC, Drapkin R, Livingston DM, Liu JF. An activated ErbB3/NRG1 autocrine loop supports in vivo proliferation in ovarian cancer cells. *Cancer Cell*. 2010;17:298–310.
60. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Janne PA. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316:1039–43.
61. Huang S, Li C, Armstrong EA, Peet CR, Saker J, Amler LC, Sliwkowski MX, Harari PM. Dual targeting of EGFR and HER3 with MEHD7945A overcomes acquired resistance to EGFR inhibitors and radiation. *Cancer Res*. 2013;73:824–33.
62. Bianco R, Shin I, Ritter CA, Yakes FM, Basso A, Rosen N, Tsurutani J, Dennis PA, Mills GB, Arteaga CL. 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.
63. Sergina NV, Rausch M, Wang D, Blair J, Hann B, Shokat KM, Moasser MM. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature*. 2007;445:437–41.
64. 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.
65. Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, Ercan D, Rogers A, Roncalli M, Takeda M. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Sci Transl Med*. 2011;3:99ra86.
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, Esteva FJ, Liu B. Heterotrimerization of the growth factor receptors erbB2, erbB3, and insulin-like growth factor-1 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, Thor AD. 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, Liu B. 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, Lofgren JA, Tindell C, Evans DP, Maiese K, Scher HI, Sliwkowski MX. 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-1 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-1 receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Res*. 2005;65:11118–28.
75. 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.
76. Gala K, Chandrapaty S. Molecular pathways: HER3 targeted therapy. *Clin Cancer Res*. 2014;20:1410–6.
77. Mujoo K, Choi BK, Huang Z, Zhang N, An Z. Regulation of ERBB3/HER3 signaling in cancer. *Oncotarget*. 2014;5:10222–36.
78. Schoeberl B, Faber AC, Li D, Liang MC, Crosby K, Onsum M, Burenkova O, Pace E, Walton Z, Nie L, Fulgham A, Song Y, Nielsen UB, Engelman JA, Wong KK. An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. *Cancer Res*. 2010;70:2485–94.
79. Schoeberl B, Pace EA, Fitzgerald JB, Harms BD, Xu L, Nie L, Linggi B, Kalra A, Paragas V, Bukhalid R, Grantcharova V, Kohli N, West KA, Leszczyniecka M, Feldhaus MJ, Kudla AJ, Nielsen UB. Therapeutically targeting ErbB3: a key node in ligand-induced activation of the ErbB receptor-PI3K axis. *Sci Signal*. 2009;2:ra31.
80. Jiang N, Saba NF, Chen ZG. Advances in targeting HER3 as an anticancer therapy. *Chemother Res Pract*. 2012;2012:817304.
81. Mishra R, Patel H, Alanazi S, Yuan L, Garrett JT. HER3 signaling and targeted therapy in cancer. *Oncol Rev*. 2018;12:355.
82. Aurisicchio L, Marra E, Luberto L, Carlomosti F, De Vitis C, Noto A, Gunes Z, Roscilli G, Mesiti G, Mancini R, Alimandi M, Ciliberto G. Novel anti-ErbB3 monoclonal antibodies show therapeutic efficacy in xenografted and spontaneous mouse tumors. *J Cell Physiol*. 2012;227:3381–8.
83. 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.
84. McDonagh CF, Huhlov A, Harms BD, Adams S, Paragas V, Oyama S, Zhang B, Luus L, Overland R, Nguyen S, Gu J, Kohli N, Wallace M, Feldhaus MJ, Kudla AJ, Schoeberl B, Nielsen UB. 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.
85. Jacob W, James I, Hasmann M, Weisser M. Clinical development of HER3-targeting monoclonal antibodies: perils and progress. *Cancer Treat Rev*. 2018;68:111–23.
86. Arnett SO, Teillaud J-L, Wurch T, Reichert JM, Dunlop DC, Huber M. MAbs. 2011;3:133–52.
87. Shimizu T, Yonesaka K, Hayashi H, Iwasa T, Haratani K, Yamada H, Ohwada S, Kamiyama E, Nakagawa K. 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;79:489–95.
88. Yonesaka K, Hirotsu K, Kawakami H, Takeda M, Kaneda H, Sakai K, Okamoto I, Nishio K, Janne PA, Nakagawa K. 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.
89. Huang J, Wang S, Lyu H, Cai B, Yang X, Wang J, Liu B. 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.
90. Wang S, Huang J, Lyu H, Cai B, Yang X, Li F, Tan J, Edgerton SM, Thor AD, Lee CK, Liu B. Therapeutic targeting of erbB3 with MM-121/SAR256212 enhances antitumor activity of paclitaxel against erbB2-overexpressing breast cancer. *Breast Cancer Res*. 2013;15:R101.
91. Liu JF, Ray-Coquard I, Selle F, Poveda AM, Cibula D, Hirte H, Hilpert F, Raspagliesi F, Gladieff L, Harter P, Siena S, Del Campo JM, Tabah-Fisch I, Pearlberg J, Moyo V, Riahi K, Nering R, Kubasek W, Adiwijaya B, Czibere A, Naumann RW, Coleman RL, Vergote I, MacBeath G, Pujade-Lauraine E. 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.
92. Schoeberl B, Kudla A, Masson K, Kalra A, Curley M, Finn G, Pace E, Harms B, Kim J, Kearns J, Fulgham A, Burenkova O, Grantcharova V, Yazar D, Paragas V, Fitzgerald J, Wainszelbaum M, West K, Mathews S, Nering R, Adiwijaya B, Garcia G, Kubasek B, Moyo V, Czibere A, Nielsen UB, MacBeath G. 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.
93. Mirschberger C, Schiller CB, Schraml M, Dimoudis N, Friess T, Gerdes CA, Reiff U, Lifke V, Hoelzlwimmer G, Kolm I, Hopfner KP, Niederfellner G, Bossenmaier B. RG7116, a therapeutic antibody that binds the inactive HER3 receptor and is optimized for immune effector activation. *Cancer Res*. 2013;73:5183–94.
94. Sala G, Traini S, D'Egidio M, Vianale G, Rossi C, Piccolo E, Lattanzio R, Piantelli M, Tinari N, Natali PG, Muraro R, Iacobelli S. 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.
95. Sala G, Rapposelli IG, Ghasemi R, Piccolo E, Traini S, Capone E, Rossi C, Pelliccia A, Di Risio A, D'Egidio M, Tinari N, Muraro R, Iacobelli S. 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.

96. Foreman PK, Gore M, Kobel PA, Xu L, Yee H, Hannum C, Ho H, Wang SM, Tran HV, Horowitz M, Horowitz L, Bhatt RR. ErbB3 inhibitory surroboodies inhibit tumor cell proliferation in vitro and in vivo. *Mol Cancer Ther.* 2012; 11:1411–20.
97. Schwarz LJ, Hutchinson KE, Rexer BN, Estrada MV, Gonzalez Ericsson PI, Sanders ME, Dugger TC, Formisano L, Guerrero-Zotano A, Red-Brewer M, Young CD, Lantto J, Pedersen MW, Kragh M, Horak ID, Arteaga CL. An ERBB1–3 Neutralizing Antibody Mixture With High Activity Against Drug-Resistant HER2+ Breast Cancers With ERBB Ligand Overexpression. *J Natl Cancer Inst.* 2017;109(11). <https://doi.org/10.1093/jnci/djx065>.
98. Osada T, Hartman ZC, Wei J, Lei G, Hobeika AC, Gwin WR, Diniz MA, Spector N, Clay TM, Chen W, Morse MA, Lysterly HK. Polyfunctional anti-human epidermal growth factor receptor 3 (anti-HER3) antibodies induced by HER3 vaccines have multiple mechanisms of antitumor activity against therapy resistant and triple negative breast cancers. *Breast Cancer Res.* 2018;20:90.
99. Iorio MV, Casalini P, Piovani C, Di Leva G, Merlo A, Triulzi T, Menard S, Croce CM, Tagliabue E, et al. *Cancer Res.* 2009;69:2195–200.
100. Scott GK, Goga A, Bhaumik D, Berger CE, Sullivan CS, Benz CC. Coordinate suppression of ERBB2 and ERBB3 by enforced expression of micro-RNA miR-125a or miR-125b. *J Biol Chem.* 2007;282:1479–86.
101. Wang S, Huang J, Lyu H, Lee CK, Tan J, Wang J, Liu B. Functional cooperation of miR-125a, miR-125b, and miR-205 in entinostat-induced downregulation of erbB2/erbB3 and apoptosis in breast cancer cells. *Cell Death Dis.* 2013;4:e556.
102. Altieri DC. Survivin, cancer networks and pathway-directed drug discovery. *Nat Rev Cancer.* 2008;8:61–70.
103. Mita AC, Mita MM, Nawrocki ST, Giles FJ. Survivin: key regulator of mitosis and apoptosis and novel target for Cancer therapeutics. *Clin Cancer Res.* 2008;14:5000–5.
104. Coumar MS, Tsai FY, Kanwar JR, Sarvagalla S, Cheung CH. Treat cancers by targeting survivin: just a dream or future reality? *Cancer Treat Rev.* 2013;39: 802–11.
105. Huang J, Lyu H, Wang J, Liu B. MicroRNA regulation and therapeutic targeting of survivin in cancer. *Am J Cancer Res.* 2015;5:20–31.
106. Schulze WX, Deng L, Mann M. Phosphotyrosine interactome of the ErbB-receptor kinase family. *Mol Syst Biol.* 2005;1:2005.0008.
107. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. *Nat Rev Drug Discov.* 2017;16: 203–22.
108. Nana-Sinkam SP, Croce CM. Clinical applications for microRNAs in cancer. *Clin Pharmacol Ther.* 2013;93:98–104.
109. Bader AG, Brown D, Winkler M. The promise of microRNA replacement therapy. *Cancer Res.* 2010;70:7027–30.
110. Cho WC. MicroRNAs as therapeutic targets and their potential applications in cancer therapy. *Expert Opin Ther Targets.* 2012;16:747–59.
111. Taipaleenmaki H, Browne G, Akech J, Zustin J, van Wijnen AJ, Stein JL, Hesse E, Stein GS, Lian JB. Targeting of Runx2 by miR-135 and miR-203 impairs progression of breast Cancer and metastatic bone disease. *Cancer Res.* 2015;75:1433–44.
112. Catela Ivkovic T, Voss G, Cornella H, Ceder Y. microRNAs as cancer therapeutics: a step closer to clinical application. *Cancer Lett.* 2017;407:113–22.
113. Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee SS. Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine. *Mol Ther Nucleic Acids.* 2017;8:132–43.

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