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Development of new estrogen receptor-targeting therapeutic agents for tamoxifen-resistant breast cancer

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Abstract

Despite our deepening understanding of the mechanisms of resistance and intensive efforts to develop therapeutic solutions to combat resistance, *de novo* and acquired tamoxifen resistance remains a clinical challenge, and few effective regimens exist to treat tamoxifen-resistant breast cancer. The complexity of tamoxifen resistance calls for diverse therapeutic approaches. This review presents several therapeutic strategies and lead compounds targeting the estrogen receptor signaling pathways for treatment of tamoxifen-resistant breast cancer, with a critical assessment of challenges and potentials regarding clinical outcome. Medicinal chemistry holds the key to effective, personalized combination therapy for tamoxifen-resistant breast cancer by making available a diverse arsenal of small-molecule drugs that specifically target signaling pathways modulating hormone resistance. These combination therapy candidates should have the desired specificity, selectivity and low toxicity to resensitize tumor response to tamoxifen and/or inhibit the growth and proliferation of resistant breast cancer cells.

Breast cancer & tamoxifen resistance

Breast cancer is the most common malignancy in women worldwide, comprising 16% of all female cancers. It is estimated that more than 1.6 million new cases of breast cancer occurred among women worldwide in 2010 [1]. A total of 519,000 women died in 2004 due to breast cancer [101]. The National Cancer Institute estimates that approximately 232,340 new case of breast cancer are expected in the USA in 2013. It is the second-leading cause of cancer death among American women, claiming nearly 40,030 lives in 2013 alone [102–103]. Approximately 70% of all diagnosed breast cancers express the estrogen receptor (ER) [2]. ER-positive (ER+) breast cancer depends on the hormone estrogen for growth and proliferation. This involves both genomic (nuclear) and non-genomic (extranuclear) pathways. Genomic pathways include the classical interactions of ligand-bound ER dimers with estrogen-responsive elements in target gene promoters. The nongenomic pathways involve the rapid and transient activation of several kinase cascades mediated by the translocation of ‘nuclear’ receptors to the cytoplasmic side of the cell membrane [3]. **Selective ER modulators (SERMs)** interfere with ER-regulated signaling pathways by competing with estrogen in binding to ER. Tamoxifen (**1**), the pioneering SERM, has been

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used ubiquitously in clinical practice over the last 30 years for the treatment of breast cancer and is currently available to reduce the risk of breast cancer in high-risk woman.

Tamoxifen can work as a wonder drug, inhibiting cancer growth and shrinking tumors without the severe side effects often associated with chemotherapy [4–5]. Unfortunately, 30–40% of patients who take tamoxifen become resistant to endocrine therapy within 3–5 years [6]. This acquired resistance occurs when the disease progresses despite continuing tamoxifen treatment [5,7]. ER+ breast cancer can escape antiestrogen actions by upregulating other signaling pathways involved in cell survival and proliferation. Enhanced signaling via growth factor receptors, such as EGF receptor (EGFR) [8] and HER receptor 2 (HER2) [9], has been implicated in the acquired resistance to endocrine therapy. The cross-talk between ER and such alternative signaling pathways are believed to enable breast cancer survival when challenged by antiestrogens agents [10]. This knowledge has led to numerous treatment strategies combining endocrine and targeted inhibitor therapies. For example, clinical trials of everolimus [11–12] in combination with endocrine therapies have yielded promising results and resulted in the first m-TOR inhibitor drug to be approved by US FDA and European Medicines Agency for post-menopausal women with advanced hormone-receptor positive, HER2-negative breast cancer. Other preclinical or clinical studies have demonstrated promising results. For instance, an Src inhibitor partially restores response to tamoxifen in tamoxifen-resistant breast cancer cells [13–15]. The combination of Notch inhibitor and tamoxifen was reported to eliminate the emergence of tamoxifen resistance [16]. Tamoxifen and a low dose of brivanibalaninate (VEGF receptor-2/FGFR receptor-1 inhibitor) can potentially be combined to retard SERM-resistant tumor growth [17]. The combination of vorinostat (HDAC inhibitor) and tamoxifen is well tolerated and exhibits encouraging activity in reversing hormone resistance [18]. Moreira *et al.* provided a mechanistic explanation for the combination effect of tamoxifen and estradiol to induce apoptosis of tamoxifen-resistant breast cancer cells [19]. However, due to space limit, this review will focus on new therapeutic agents directly targeting the ER or the estrogen-producing enzyme.

Exploring new SERMs for treatment of tamoxifen-resistant breast cancer

One strategy for treating tamoxifen-resistant breast cancer is to use alternative SERMs that can still act to inhibit the ER signaling pathway. SERMs bind to ER and modulate its transcriptional capabilities in different ways in diverse estrogen target tissues. As a first-line treatment of ER+ breast cancer for decades, the SERM tamoxifen acts as an ER antagonist in breast tissue via its active metabolites, 4-hydroxytamoxifen (4-OHT) and endoxifen. In other tissues such as the endometrium, it behaves as an agonist and, thus, may be characterized as a mixed agonist/antagonist. Ideally, alternative SERMs should be designed and synthesized to substitute for tamoxifen in tamoxifen-resistant breast cancer. As a result of intensive research in this direction, a number of alternative SERMs, which can be further divided into ‘tamoxifen-like’ compounds (e.g., idoxifene, toremifene, ospemifene and droloxifene), and ‘fixed ring’ compounds (e.g., ERA-923, raloxifene, arzoxifene and EM-800) have been developed and tested as substitutes (Figure 1). To date, however, clinical improvement has only been modest for these SERMs.

Idoxifene (**2**) is a ‘tamoxifen-like’ SERM but demonstrated greater binding affinity for the ER and reduced agonist activity compared with tamoxifen in preclinical studies [20]. In a randomized Phase II clinical trial in 47 postmenopausal patients with progressive locally advanced/metastatic breast cancer demonstrating previous resistance to standard tamoxifen therapy, idoxifene was used at 20 mg/day in 25 patients compared with tamoxifen at 40 mg/day in 22 patients. Two partial responses and two disease stabilizations for >6 months were observed with idoxifene (overall clinical benefit rate 16%, 95% CI: 4.5–36.1%), whereas no

objective responses were observed with the increased 40 mg/day dose of tamoxifen, although two patients had disease stabilizations for 7 and 14 months (clinical benefit rate 9%, 95%, CI: 1.1–29.2%). Notably, the toxicity profile and effects of idoxifene on endocrine/lipid parameters were similar to those of tamoxifen.

Chang *et al.* [21] investigated the utility of conventional SERMs for tamoxifen-resistant breast cancer cells and found that SERMs generally demonstrated greater antiestrogenic potency in MCF-7 cells than in tamoxifen-resistant cells except toremifene (**3**) and ospemifene (**4**). In particular, toremifene was more efficacious in tamoxifen-resistant cells than in the sensitive MCF-7 cells. These results support the possibility of using toremifene for treatment of tamoxifen-resistant cancer. The effectiveness demonstrated by toremifene on tamoxifen-resistant cells might involve pathways different from apoptosis and autophagy. Further study is warranted to elucidate the underlying mechanisms of action of toremifene on tamoxifen-resistant cancer.

Another SERM, ERA-923 (**6**), was found to potently inhibit estrogen binding to ER α (IC₅₀ = 14 nM). In MCF-7 cells, ERA-923 blocks estrogen-stimulated growth (IC₅₀ = 0.2 nM) associated with cytostasis [22]. *In vitro*, an MCF-7 variant with inherent resistance to tamoxifen (tenfold) or 4-OH tamoxifen (>1000-fold) was found to retain complete sensitivity to ERA-923. Partial sensitivity to ERA-923 also existed in MCF-7 variants that have acquired profound tamoxifen resistance. In tumor-bearing animals, ERA-923 (10 mg/kg/day given orally) inhibited 17 β -estradiol-stimulated growth in human tumors derived from MCF-7, EnCa-101 endometrial, BG-1 ovarian carcinoma cells and an MCF-7-variant cell line with intrinsic resistance to tamoxifen. In comparison, raloxifene (**7**) was inactive in the MCF-7 xenograft model. Unlike tamoxifen, droloxifene (**5**) or raloxifene, ERA-923 was not uterotrophic in immature rats or ovariectomized mice. Consistent with this, tamoxifen, but not ERA-923, was found to stimulate the growth of EnCa-101 tumors. The benzothiophene arzoxifene (**8**) is a new third-generation SERM that has been shown to inhibit cell growth as effectively as tamoxifen [23]. Northern analysis revealed that arzoxifene significantly suppressed pS2 and progesterone receptor B, but stimulated the antitrypsin, mRNA expression. Unlike estradiol and tamoxifen, arzoxifene failed to induce the overexpression of cathepsin D mRNA and protein expression. As with tamoxifen, the metabolite of arzoxifene (ARZm; **9**) was a more potent growth inhibitor of MCF-7 cells than arzoxifene. A tamoxifen-resistant MCF-7 subline displayed a significant dose-dependent growth inhibition to ARZm, whereas the fulvestrant resistant cell line only responded to high concentration. The randomized, double-blind, Phase II study assessing two doses of ARZm in women with advanced breast cancer reported that there were no significant differences in efficacy or safety between 20 and 50 mg of ARZm. Response rates in the 20-mg arm were numerically higher than the 50-mg arm according to the investigator (40.5 vs 36.4%) and the independent review panel (42.9 vs 27.3%). Clinical benefit rate was higher in the 20-mg arm according to the investigator (64.3 vs 61.4%) and the independent review panel (59.5 vs 47.7%). ARZm was well tolerated. There were no study drug-related deaths. Mean observed steady-state plasma concentrations of ARZm were 3.62 and 7.48 ng/ml for the 20- and 50-mg doses, respectively [24].

A new, orally active SERM, EM-800 (**10**) (SCH-57050, precursor of acolbifene, **11**), was tested in a Phase II clinical study involving 43 post menopausal/oophorectomized women with breast cancer. These patients had received tamoxifen, either for metastatic disease or as adjuvant to surgery for 1 year, had relapsed and were treated in a prospective, multicenter study with EM-800 (20 mg/d [n = 21] or 40 mg/d [n = 22] orally). A total of 37 patients had ER+ tumors (>10 fmol/mg; mean, 146 fmol/mg cytosolic protein), three patients had ER-negative/progesterone receptor-positive tumors, and three patients had undetermined ER status. The objective response rate to EM-800 was 12%, with one complete response and

four partial responses. Ten patients (23%) had stable disease for 3 months, and seven patients (16%) had stable disease for 6 months. With a median follow-up of 29 months, median duration of response was 8 months (range, 7–71+ months). Treatment with EM-800 was well tolerated. No significant adverse events related to the study drug were observed clinically or biochemically. EM-800 produced responses in a significant proportion of patients with tamoxifen-resistant breast cancer, thus, demonstrating that this highly potent, SERM, which lacks estrogenic activity in the mammary gland and endometrium, has incomplete cross-resistance with tamoxifen, thus, suggesting additional benefits in the treatment of breast cancer [25].

Lasofloxifene (**12**), a third-generation SERM, was used in the PEARL trial, a double-blind, placebo-controlled, randomized trial. A total of 8556 postmenopausal women with low bone density and normal mammograms were randomly assigned to two doses of lasofloxifene – either 0.25 or 0.50 mg per day, or placebo. Compared with the placebo, 0.5 mg of lasofloxifene significantly reduced the risk of total breast cancer by 79% and ER+ invasive breast cancer by 83%. It may have some potential benefit for tamoxifen-resistant cancers. Furthermore, there was a 32% reduction in coronary events, and a 36% reduction in strokes. Vertebral and nonvertebral fractures decreased by 42 and 24%, respectively. The risk reduction for breast cancer with lasofloxifene was similar to that reported for tamoxifen and raloxifene. At the same time, lasofloxifene did not pose a risk for other cancers, as opposed to tamoxifen, which is associated with an increased risk of endometrial cancer and other gynecological safety concerns [26]. Although a number of SERMs have been reported to have good efficacy in treatment of tamoxifen-resistant breast cancer *in vitro* and *in vivo*, there is much to be desired before a clinically useful SERM becomes available [27]. The prospect of a novel, alternative SERM that acts through somewhat different ER-regulated signaling pathway is limited, because most acquired tamoxifen resistance is accompanied by estrogen independence with either downregulated ER signaling or enhanced alternative survival signaling. Thus, it is not surprising that most known SERMs have demonstrated a high level of cross-resistance with tamoxifen [28–31].

Selective estrogen downregulators for treatment of tamoxifen-resistant breast cancer

A significant number of breast cancers remain ER+ after prolonged treatment with tamoxifen and after they become tamoxifen resistant. Thus, while the utility of a different SERM is diminished, response to selective estrogen down regulators (SERDs), such as the prototype fulvestrant, is still possible. The only approved SERD, fulvestrant (**13**), is a novel ER antagonist that binds to and degrades ER and its signaling pathways (Figure 2). It is not associated with tamoxifen-like agonist effects, not cross-resistant to tamoxifen or **aromatase inhibitors (AIs)**, and produces higher response rates than other SERMs. Fulvestrant has been found as effective as anastrozole in the treatment of postmenopausal women with advanced breast cancer, whose disease has progressed on prior adjuvant tamoxifen therapy [32,33]. Unfortunately, the clinical outcome with fulvestrant has been rather disappointing due to its poor bioavailability and low levels of the drug at the tumor to affect a quantitative turnover of the receptor [34,35]. Thus, developing new SERDs with improved pharmaceutical properties remains an attractive strategy for combating SERM resistance.

Initially known as a SERM, GW5638 (**14**) was found to exhibit a mode of action that resembles a SERD by destabilizing ER. Its bioavailable metabolite, GW7604 (**15**), was demonstrated to be a promising SERD for treatment of tamoxifen-resistant breast cancer [36]. Discovered by Willson and colleagues in 1994, GW5638 contains a shorter allylcarboxylic group, instead of the normal tertiary amino side chain, on a triphenylethylene structural motif. The crystal structure of the ER α ligand-binding domain (LBD) bound to the

structurally similar compound GW5638, which has therapeutic potential and does not stimulate the uterus, show GW5638 relocates the carboxy-terminal helix (H12) to the known coactivator-docking site in the ER α LBD, as does tamoxifen. However, GW5638 repositions residues in H12 through specific contacts with the N terminus of this helix. In contrast to tamoxifen, the resulting increase in exposed hydrophobic surface of ER α LBD correlates with a significant destabilization of ER α in MCF-7 cells. Thus, the GW5638–ER α LBD structure reveals an unexpected mode of SERM-mediated ER antagonism, in which the stability of ER α is decreased through an altered position of H12. This dual mechanism of antagonism may explain why GW5638 can inhibit tamoxifen-resistant breast tumors [37].

Starting with GW-7604, the hydroxylated metabolite of GW-5638, Kieser *et al.* investigated how alterations in both the ligand core structure and the appended acrylic acid substituent affect its SERD activity. The new ligands were based on high-affinity, symmetrical cyclofenil or bicyclo[3.3.1]nonane core systems, and in these, the position of the carboxyl group was extended from the ligand core, either retaining the vinylic linkage of the substituent or replacing it with an ether linkage. Although most structural variants demonstrated binding affinities for ER α and ER β higher than that of GW-7604, only the cyclofenil analog and bicyclononane analog preserving the acrylic acid side chain of the compound retained SERD activity, although they could possess varying core structures. Hence, the acrylic acid moiety of the ligand is crucial for SERD-like blockade of ER activities. Therefore, the cyclofenil analog (**16**) and bicyclononane analog (**17**) of the compound are promising therapeutic agents for the treatment of hormone refractory breast cancer [38].

Recently, Yoneya *et al.* identified a new orally active nonsteroidal SERD, CH4986399 (**18**), which is structurally unrelated to fulvestrant or tamoxifen [39]. The oral antitumor activity and downregulation of ER by CH4986399 were examined in human breast cancer Br-10 and ZR-75-1 xenografts. The study found that tumor weight in the Br-10 xenograft model was significantly reduced by CH4986399 (100 mg/kg orally [p.o.]) as well as fulvestrant (3 mg/body subcutaneously [sc.]). In the ZR-75-1 xenografts, CH4986399 (100 mg/kg p.o.) treatment resulted in much smaller tumor weight and decreased ER content without agonistic activity. These results suggest that this chemical structurally distinct SERD, CH4986399, may help overcome drug resistance from the endocrine treatment sequence for breast cancer patients.

Two new pure antiestrogen agents, ZK-703 (**19**) and ZK-253 (**20**), have been reported by Hoffmann *et al.* as having antiestrogenic effects on the growth of estrogen-dependent breast tumors *in vivo* in several mouse xenograft models [40]. ZK-703 (administered sc.) and ZK-253 (administered p.o.) were more effective than tamoxifen or fulvestrant in inhibiting the growth of ER+ breast cancer in all xenograft models. For example, MCF-7 tumors relapsed (i.e., reached the size threshold) in 10 weeks in mice treated with tamoxifen but in 30 weeks in mice treated with ZK-703. ZK-703 and ZK-253 also prevented further tumor progression in tamoxifen-resistant breast cancer models to a similar extent (>30 weeks in mice with ZR75-1 and MCF7/TAM tumors). In the chemically induced rat breast cancer models, p.o. administered ZK-703 and ZK-253 caused a nearly complete (>80%) inhibition of tumor growth. ER levels were dramatically reduced in MCF7 tumors after 5 weeks of ZK-703 treatment compared with ER levels in vehicle-treated tumors. By contrast, ER levels in tamoxifen-treated tumors were higher than those in control tumors. ZK-703 and ZK-253 are potent, long-term inhibitors of growth in both tamoxifen-sensitive and -resistant breast cancer models.

Development of AIs for treatment of tamoxifen-resistant breast cancer

Hormonal therapy with AIs is now standard treatment for postmenopausal women with ER+ breast cancer, both as adjuvant therapy and in the treatment of advanced disease. AIs block estrogen production by inhibiting or inactivating aromatase to inhibit the growth of breast tumors. Three FDA-approved AIs are currently available: anastrozole (**21**), exemestane (**22**) and letrozole (**23**; Figure 3) [41,204]. Several Phase III clinical trials have been conducted where patients with tamoxifen-resistant metastatic breast cancer were treated with these AIs [42–46]. Compared with the standard second-line treatment of megestrol acetate, three of these trials reached a significant advantage by using AIs. Thus, the AIs can be used as effective second-line therapy for breast cancer with acquired resistance to tamoxifen. Moreover, the steroidal AIs (e.g., exemestane) did not demonstrate cross-resistance with the nonsteroidal AIs (e.g., anastrozole and letrozole), suggesting that sequential use of the steroidal and nonsteroidal AIs may offer prolonged clinical benefit [47,48].

Recently, Ghosh *et al.* have designed novel C6-substituted androsta-1,4-diene-3,17-dione AIs by targeting an androgen-specific active site revealed in the crystal structure of human placental [49]. Several of the C6-substituted 2-alkynyloxy compounds inhibit purified placental aromatase with IC₅₀ values in the nanomolar range (**27**, 11.8 nM; **31**, 20.0 nM). Antiproliferation studies in a MCF-7 breast cancer cell line demonstrate that some of these compounds have EC₅₀ values >1 nM, exceeding that for exemestane. x-ray structures of aromatase complexes of two potent compounds reveal that, per their design, the novel side groups protrude into the opening to the access channel unoccupied in the enzyme–substrate/exemestane complexes. The observed structure–activity relationship is borne out by the x-ray data. Structure-guided design permits utilization of the aromatase-specific interactions for the development of next-generation AIs that could potentially be used as second-line therapy for tamoxifen-resistant breast cancers.

Other new agents for the treatment of tamoxifen-resistant breast cancer

Despite advances made in recent years in the development of SERMs, SERDs and AIs for the treatment of tamoxifen-resistant breast cancer, clinical successes have been limited, underscoring the urgent therapeutic need to overcome, delay or contain metastatic progression after the disease no longer responds to tamoxifen treatment. Novel therapeutic approaches include developing ligands that target the ER signaling pathway by different mechanisms of action toward ER. For example, TAS-108 (**32**; Figure 4), representing a novel class of synthetic ER ligands [50] blocked both ER transactivation functions without inhibiting DNA-binding activity. While TAS-108 exhibited pure antagonistic activity as it blocked both the N-terminal AF-1 and C-terminal AF-2 transactivation functions, it also promoted the recruitment of the silencing mediator of retinoic acid and thyroid hormone receptor co-repressor that abolished ER transactivation function without inhibition of the ability of ER α to bind to its target DNA [51]. Moreover, both TAS-108 and fulvestrant acted as antagonists for the transactivation functions of the D351Y mutant, derived from tamoxifen-resistant breast cancer cells, while estrogen and known SERMs, 4-OH tamoxifen and raloxifene, stimulated D351Y-mediated transcription. The observation that TAS-108 acts as a novel estrogen antagonist that recruits co-repressors to ERs without AF-1 activation or prevention of DNA binding raises the possibility of using TAS-108 as an effective agent against tamoxifen-resistant breast cancer via a different mechanism than that for fulvestrant [51]. In a Phase II clinical trial where 15 patients received p.o. administered TAS-108, there were observed clinical benefits in five patients [52,53]. Importantly, TAS-108 was well tolerated at doses up to 120 mg and did not cause notable changes either in hormone levels or bone metabolism markers.

In another mechanism-based development, the electrophile disulfide benzamide (DIBA; **33**; Figure 5) was utilized as an ER zinc finger inhibitor that blocks ligand-dependent and -independent cell growth of tamoxifen-resistant breast cancer *in vitro* and *in vivo* [54]. The mechanism of action involves the functional inhibition of zinc fingers in the ER DNA-binding domain, thereby selectively blocking binding of the ER to its responsive element and subsequent transcription. As a result, estrogen-stimulated cell proliferation is markedly reduced by DIBA. It was further confirmed that phosphorylation of HER2, MAPK, AKT and AIB1 was not perturbed by DIBA, suggesting that DIBA-modified ER α may induce a switch from agonistic to antagonistic effects of tamoxifen on resistant breast cancer cells [54–56]. Thus, targeting the ER zinc finger may offer a unique mechanism to alter the activity of the ER in the case of tamoxifen resistance.

Koren and colleagues reported that YM-1 (**34**), a derivative of MKT-077 (a rhodacyanine dye; **35**; Figure 6), was more cytotoxic and localized differently than MKT-077 across multiple cancer cell lines [57]. This toxicity was limited to cancer cell lines. Brief treatment with YM-1 restored tamoxifen sensitivity to a refractory tamoxifen-resistant MCF7 cell model. This effect is potentially due to altered ER α phosphorylation, an outcome precipitated by selective reductions in Akt levels (Akt/PKB). Thus, modifications to the rhodacyanine scaffold could potentially be made to improve efficacy and pharmacokinetic properties. Moreover, the impact on tamoxifen sensitivity could be a new utility for this compound family.

Therapeutic solutions for *de novo* (intrinsic) tamoxifen-resistant breast cancer

Up to 30% of ER+ breast cancer does not respond to SERM treatment initially [58]. Clinically, metastatic breast cancers that are ER+ and PR-positive are approximately 80% responsive to tamoxifen therapy, whereas tumors that are ER+ but PR-negative are only 40% responsive to anti-hormonal therapy [59]. The mechanism of intrinsic resistance is not fully understood, but one possibility lies in the polymorphism of the cytochrome P450 enzyme, CYP2D6, which is responsible for converting tamoxifen into its active metabolites, 4-OHT, **36** and endoxifen (**37**), both of which are 30–100-times more potent than tamoxifen [60–62]. Existing clinical and laboratory data support the idea that bioavailable 4-OHT and endoxifen could offer improved therapeutic benefit with lower dose requirements and reduced hot flash and other side effects [63–65]. Another possible mechanism was that overexpression of the HER2 may play an important role in intrinsic tamoxifen-resistant breast cancer [66]. For intrinsic resistance whose mechanisms could involve other aberrant signaling pathways, there have been efforts to develop alternative therapeutic approaches to:

- Sensitize tumor response to tamoxifen or other SERMs;
- Identify other effective targets;
- Develop combination therapies for *de novo* resistance.

To overcome *de novo* resistance due to CYP2D6 polymorphism, Jiang *et al.* used a boron-based prodrug strategy to design and synthesize three boronic derivatives (**38–40**; Figure 7) of tamoxifen [65]. The rationale for this approach is that the boron-aryl carbon bond is susceptible to oxidative cleavage by hydrogen peroxide to form a phenol compound. The results demonstrate that the bioisosteres inhibit the growth of two ER+ breast cancer cells, MCF-7 and T47D with potencies comparable with or greater than that of 4-OHT. The study suggests that boron-based 4-OHT bioisosteres may be an effective therapeutic remedy to intrinsic tamoxifen resistance in breast cancer patients deficient in CYP2D6 metabolism.

Neo-tanshinlactone (**41**) and its analogs, such as **42**, are potent and selective anti-breast cancer agents *in vitro* compared with tamoxifen citrate. It was tenfold more potent and 20-fold more selective than tamoxifen against ER+ and HER2++ breast cancer cells. Several derivatives (**43–46**; Figure 8) exerted potent and selective antibreast cancer activity with IC₅₀ values of 0.3, 0.2, 0.1 and 0.1 µg/ml, respectively, against the ZR-75-1 cell line (ER+, HER2++). Compound **46** was two- to three-fold more potent than **41** against ZR-75-1 and SK-BR-3 (ER-, HER2++), respectively. Importantly, **45** exhibited high selectivity with 23 times greater potency against ZR-75-1 than MCF-7. Compound **44** had an approximately 12-fold ratio of SK-BR-3/MCF-7 selectivity. In addition, analog **42** showed potent activity against a ZR-75-1 xenograft model, but not PC-3 and MDA-MB-231 (ER-negative) xenografts, as well as high selectivity against breast cancer cells compared with normal breast tissue-derived cell lines. Thus, **43–46** can serve as lead compounds for further development of clinical trial candidates for treatment of *de novo* tamoxifen-resistant breast cancer [67–69].

Future perspective

Due to the heterogeneity of breast cancer, tamoxifen resistance has manifested both common molecular signatures and individual phenotypic traits that account for the eventual failure of hormone therapy. Thus, understanding the precise mechanism of resistance in individual patients is critical to designing effective treatment plans. Use of alternative SERMs, shifting to second-line treatment by SERDs and AIs, or turning to ER ligands with different modes of action will most probably achieve clinical success when targeting small cohorts of patients with well-characterized and well-defined genetic biomarkers that predict therapy responses. Most acquired resistance to tamoxifen therapy is accompanied by the activation of alternative survival signaling, such as those regulated by HER2, EGFR and IGFR. However, which specific pathway, or multiple pathways may be at work could differ from patient to patient, making a single combination therapy less probable to have universally satisfactory treatment response. Availability of selective kinase inhibitors for sequential or simultaneous use could help enhance the effectiveness of targeted combination therapy if a personalized treatment approach is adopted based on the comprehensive knowledge regarding the molecular signatures of the individual. The need to discover novel SERMs and SERDs is obvious, because tamoxifen-resistant breast tumors generally retain the expression of ER, and respond to ER interferences in ways distinct from that of tamoxifen. But, perhaps, more importantly, medicinal chemistry holds the key to effective, personalized combination therapy for tamoxifen-resistant breast cancer by making available a diverse arsenal of small-molecule drugs that specifically target signaling pathways modulating hormone resistance. Based upon what we already know regarding the mechanisms of tamoxifen resistance, these combination therapy candidates sought after by medicinal chemistry should have the desired specificity, selectivity, and low toxicity to resensitize tumor response to tamoxifen and/or inhibit the growth and proliferation of resistant breast cancer cells. For such personalized therapy to succeed, however, accurate prognostic markers would be required with clinical validations, and clinical trials for new drugs should measure the attenuation of tamoxifen resistance as one of the endpoints, with results closely linked to specific predictive biomarkers.

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Key Term

Selective estrogen receptor modulators	Estrogenic compounds that selectively inhibit or stimulate estrogen-like action in various tissues, that is, mixed agonists/antagonistics (agonistic in some tissues while antagonist in others).
Aromatase inhibitors	Compounds blocking estrogen production by inhibiting or inactivating aromatase to inhibit the growth of breast tumors

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Executive summary

- The selective estrogen receptor (ER) modulator tamoxifen has been the mainstay therapeutic regimen for ER-positive (ER+) breast cancer for several decades. However, *de novo* and acquired tamoxifen resistance remains a major clinical challenge in the course of hormone therapy that has few effective remedies. The molecular complexity of tamoxifen resistance requires the availability of diverse treatment strategies. Clinically ER+ breast cancer often retains the expression of ER after acquired resistance to tamoxifen, therefore, targeting the ER may still represent a viable intervention strategy for the resistant disease.
- Alternative selective ER modulators (SERMs) can be designed and synthesized to substitute for tamoxifen against resistant breast cancer, provided that the tumor still relies on ER-regulated survival signaling. To this end, two classes of SERMs, tamoxifen-like and fixed-ring compounds have been developed and tested, some of which have made it into Phase I and Phase II clinical trials.
- While the utility of alternative SERMs may be diminished due to cross-resistance, response to selective estrogen downregulators (SERDs) such as the prototype fulvestrant is still possible for breast cancers that remain ER+. To overcome the poor bioavailability of the only clinically approved SERD, fulvestrant, a number of novel SERDs have been reported, both nonsteroidal and steroidal. These developments offer potential second-line regimens for tamoxifen-resistant breast cancer.
- While aromatase inhibitors (AIs) have become standard therapy for postmenopausal woman with ER+ breast cancer, the use of AIs as second-line treatment for tamoxifen-resistant breast cancer has yet to be proven clinically. Phase III clinical trials conducted using three US FDA-approved AIs have reported promising results with significant response from patients no-longer responding to tamoxifen. Ongoing development of next-generation AIs may provide a wider range of choices for AIs that can be used as treatment of tamoxifen-resistant breast cancer.
- In addition to advances in the use of SERMs, SERDs and AIs for the treatment of tamoxifen-resistant breast cancer, novel therapeutic approaches targeting ER signaling pathways via different mechanisms continue to be explored. These include ER ligands that can block both AF-1 and AF-2 transactivation functions of ER and those targeting the ER zinc finger.
- Intrinsic tamoxifen resistance represents approximately 30% of all diagnosed ER+ breast cancers, a significant number to which clinical solutions are few and often ineffective. Recent development in addressing *de novo* resistance includes approaches that overcome CYP2D6 polymorphism and designing more potent and selective compounds against ER+ and HER-positive breast cancer subtypes that often respond poorly to initial tamoxifen therapy.

Figure 1.
Selective estrogen receptor modulators.

Figure 2.
Selective estrogen receptor downregulators.

Figure 3.
Aromatase inhibitors.

Figure 4.
TAS-108.

Figure 5.
DIBA.

Figure 6.
YM-1 and MKT-077.

Figure 7.
Design of prodrug for 4-hydroxytamoxifen and structure of endoxifen.

Figure 8.
Neo-tanshinlactone and its analogs.