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Oral selective estrogen receptor downregulators (SERDs) a breakthrough endocrine therapy for breast cancer

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Abstract

Drugs that inhibit estrogen receptor alpha (ERα) or which block the production of estrogens remain frontline interventions in the treatment and management of breast cancer at all stages. However, resistance to endocrine therapies, especially in the setting of advanced disease, remains an impediment to durable clinical responses. Although the mechanism(s) underlying resistance to existing agents are complex, preclinical studies suggest that selective estrogen receptor downregulators (SERDs), molecules which eliminate ERα expression, may have particular utility in the treatment of breast cancers that have progressed on tamoxifen and/or aromatase inhibitors. The discovery and development of orally bioavailable SERDs provides the opportunity to evaluate the utility of eliminating ERα expression in advanced metastatic breast cancers.

There are numerous reports describing the pharmacological and therapeutic activity of small molecules that target key regulatory nodes in signaling pathways of pathological importance in breast cancer. Among the most promising of these new drugs are those that inhibit mTOR or cdk4/6.[1, 2] Notwithstanding the recent clinical success of these newer targeted therapies, it is unlikely that they will have as significant an impact on the pharmacotherapy of estrogen receptor (ER) positive breast cancer as drugs that interfere with the estrogen signaling axis. Of these, tamoxifen, a selective estrogen receptor modulator (SERM) and the aromatase inhibitors (i.e. letrozole), drugs developed over 25 years ago, remain frontline interventions in the management of ER positive disease. However, *de novo* and acquired resistance remains an impediment to durable responses in patients on these established endocrine therapies.

Until recently, treatment failure in patients taking tamoxifen or an aromatase inhibitor was considered to herald the end of the utility of targeting the ERα signaling axis in breast cancer. This contention was supported by the lack of clinical activity of a wide range of structurally diverse SERMs in endocrine resistant disease.[3, 4] However, in recent years, the field has made considerable progress towards understanding the molecular pharmacology of ERα and how changes in key pathways that impact ER action contribute to endocrine resistance. It is now well established that ERα remains engaged in advance disease, contributes to disease pathogenesis, and remains a viable therapeutic target. This

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contemporary view of ERα action in breast cancer led to the development of ICI182,780 (fulvestrant) a high affinity competitive antagonist of ERα which also targets the receptor for proteasome-dependent degradation **(Table 1)**[5]. Reflecting its distinct pharmacological profile, fulvestrant is now considered to be a first-in-class selective estrogen receptor downregulator (SERD). Unfortunately, fulvestrant has significant pharmaceutical liabilities (requiring intramuscular injection) which have negatively impacted its widespread use.[6] Regardless, the positive clinical activity of fulvestrant and studies of its mechanism of action have informed approaches to develop second (and third) generation SERDs, some of which are now undergoing clinical evaluation. The orally bioavailable drug described by Lai et al in this issue, GDC-0810 (ARN-810), is the most advanced of the next generation SERDs and is currently being evaluated in clinical trials in breast cancer patients who have progressed on standard endocrine therapy.[7] A brief discussion of the science underlying the discovery of GDC-0810 will help to explain the considerable optimism for the clinical success of this drug, and others in the same class, in patients with breast cancer. Early models describing the pharmacology of ER were quite simple. In brief, it was held that in the absence of hormone the receptor was maintained in an inactive state through its association with a large heat-shock protein complex within the cytoplasm. Agonist binding induced a conformational change in the receptor resulting in its dimerization, nuclear translocation, and subsequent interaction with specific DNA sequences within the regulatory regions of target genes. It was inferred from this simple “on/off” model that all agonists, when corrected for affinity, were equivalent and that antagonists functioned simply by competitively inhibiting agonist binding freezing the receptor in an inactive (apo) conformation.[8] Within the confines of this model, it was initially considered that tamoxifen was an ER antagonist. However, in studies first performed in rodents and subsequently in humans, it became apparent that depending on the target organ, tamoxifen could function as either an antagonist or as an agonist.[9, 10] This observation led to the reclassification of tamoxifen, and most other “ER antagonists”, as selective estrogen receptor modulators (SERMs), reflecting their tissue selective agonist/antagonist properties. The subsequent dissection of the mechanisms underlying the selective agonist/antagonist activity of SERMs resulted in a significant revision of the established model of ER pharmacology. The three most important tenets of the updated model are: (1) the overall shape of ER is influenced by the nature of the ligand to which it is bound, (2) receptor conformation influences the presentation of protein-protein interaction surfaces that allow it to interact with either positive or negative acting “coregulators”, and (3) the functional activity of coregulators differs between cells. Thus, the same receptor-ligand complex can have completely different activities in different cells.[8] These findings were also informative with respect to our understanding of tamoxifen resistance in breast cancer. Initially attributed to ERα loss, increased drug metabolism, or MDR1-mediated drug efflux, it is now believed that resistance to tamoxifen results from changes in the expression (or activity) of coregulators that enable tamoxifen to manifest agonist activity[11]. Evidence in support of this model came from structural studies that revealed that upon binding tamoxifen, ERα adopted a unique conformation that resulted in the presentation of protein-protein interaction surfaces required for its partial agonist activity.[12, 13] Surprisingly, these surfaces were distinct from those presented upon binding 17β-estradiol suggesting that the tamoxifen-ERα complex was either interacting in an ectopic manner with coregulator(s) that enabled agonist activity or was

interacting in a unique way with coregulators with which ERα would normally engage. It was implied therefore that tamoxifen resistant cancers should be sensitive to ERα ligands that induced a conformational change in the receptor that did not enable the presentation of coregulator binding surfaces required for 17β-estradiol or tamoxifen agonist activity **(Figure 1)**. Conformation-based compound profiling led to the identification of GW5638, and its 4-OH metabolite, GW7604, compounds that had distinct effects on ER structure.[14, 15] Significantly, these drugs inhibited 17β-estradiol-dependent growth of ERα-positive breast tumor xenografts and more importantly were shown to be extremely effective in tumor models of tamoxifen resistance. Crytallographic analysis of the ERα-GW7604 complex revealed that the carboxylic acid group in this compound (**Table 1**) was the key "warhead" and that its direct interaction with the peptide backbone of the receptor induced a conformational change that exposed a hydrophobic surface on the receptor that targeted it for degradation.[16] This molecule was brought forward for clinical development in 2001 by Dupont Pharmaceuticals and showed promise in a Phase I trial of heavily pretreated, unselected breast cancer patients. Unfortunately, development of this drug was discontinued, a casualty of the portfolio review that accompanied the takeover of Dupont by Bristol-Myers Squibb. While disappointing, the strong functional data and the clear understanding of its mechanism of action provided a platform upon which to base screens for new chemical entities with similar SERD activity. GDC-0810 is the first of these new SERDs to emerge, however, additional compounds with structural similarity to GW5638 (e.g. AZD9496) are also currently making their way through clinical development.

As noted in Lai et al, GW5638 is a prodrug that is converted following oral delivery to its more potent metabolite GW7604.[7] The extent to which this conversion is required for clinical activity is unknown but it is likely to be important given the higher affinity of the hydroxylated metabolite. Using cross-species microsome profiling, it was determined that the conversion of GW5638 to GW7604 was variable with only ~16% conversion observed in human liver microsomes. This potential liability was mitigated in a new chemical series by modifications in the GW5638 parent molecule that led to increased potency and removed the primary site for glucuronidation, while maintaining SERD activity. The molecule selected for development, GDC-0810, has significantly improved exposure over benchmark compounds in animals, was equivalent to GW5638 in its ability to degrade ERα, and maintained the ability to inhibit the growth of tumors in a clinically relevant xenograft model of tamoxifen resistance. It seems intuitive that elimination of the need for metabolic activation would increase efficacy although the extent to which this contributes to clinical activity remains to be determined.

The results of the ongoing clinical trials with GDC-0810 are eagerly awaited as they will provide a definitive test of the utility of targeting ERα in advanced metastatic breast cancer. In the meantime the studies presented in Lai et al, and others like it, provide the framework for discussion of a variety of issues related to targeting ERα in advanced disease. One of the most hotly debated issues in the field is whether or not SERDs will have any therapeutic advantage over high affinity competitive antagonists of ERα without SERD activity. A cursory review of the clinical studies performed with several structurally different high affinity antagonists would seem to suggest that high affinity antagonists are not the answer.[3]

However, the results of only a few of the clinical trials of these drugs were ever published and thus it is not clear by what criteria (efficacy, safety, or economics) they were considered unsuccessful. It would be very useful in this regard to have available the results of the clinical studies that evaluated pipendoxifene (ERA924) and acolbifene (EM652), two high affinity ERα antagonists that were discontinued for unstated reasons. The disappointing studies with the raloxifene derivative, arzoxifene, were initially considered to indicate that high affinity antagonists would be ineffective in advanced disease.[4] However, the structure of the ERα-raloxifene complex (and by inference the arzoxifene complex) is very similar to that of the ERα-tamoxifen complex; a result that would predict cross resistance. Indeed arzoxifene was ineffective in the MCF-7 xenograft model of tamoxifen resistance, the gold standard in the field.[17] Clearly, the question of whether or not high affinity antagonists/SERMs have a place in the treatment of advanced ERα positive breast cancer remains to be determined. There is a significant body of work that would support the particular utility of a SERD. Notably, it has been demonstrated in the past in a variety of models that increased expression of coregulators or hyperactivation of signaling pathways that impact the ER-coregulator complex enables the receptor to activate target gene transcription in a ligand independent manner. These mechanisms are also thought to underlie resistance to both SERMs and to aromatase inhibitors.[18] Ligand-independent activation of ERα reduces the antagonist efficacy of SERMs while the sensitivity to SERDs is unaffected. Further, it now appears that up to 20% of tumors in metastatic, endocrine resistant breast cancer contain activating mutations in the receptor and the preclinical studies presented thus far support the idea that SERDs are viable approach to treat patients whose tumors harbor these mutations.[19] Missing from the studies of Lai et al are data describing the activity of GDC-0810 on ERα in conditions where its activity is rendered constitutively active.

A second area in breast cancer that is emerging as a priority for pharmacotherapy is breast cancer brain metastasis (BCBM). Whereas the treatment (and management) of peripheral disease has improved substantially with the advent of tamoxifen and aromatase inhibitors, there has been a dramatic increase in the incidence of BCBM [20]. Initially, it was considered that BCBM was only a significant morbidity in ERα-negative breast cancer. However, more recent studies have indicated that the prevalence of ERα-positive BCBM is considerably higher than expected [21]. This is of concern as the aromatase enzyme (cyp19) is expressed in brain and considering that the ERα-partial agonist 27-hydroxycholesterol is the most abundant oxysterol in brain.[22] There is little data on the ability of existing ER modulators and aromatase inhibitors to cross the blood brain barrier (BBB) and thus there is considerable interest in evaluating brain penetrant SERDs or SERMs in patients with BCBM. The ongoing clinical studies with GDC-0810 should be informative with respect to its ability to cross the BBB.

In addition to GDC-0810, there are several new ER modulators at various stages of development and it is reasonable to expect, given the underlying science, that several of these will be effective enough to warrant their registration as monotherapies. However, it is likely that the true potential of GDC-0810, and like compounds, will be observed in the context of drug combinations that target ERα and other signaling pathways. It has been shown for instance that resistance to HER2/EGFR inhibitors and to PI3K inhibitors is associated with increased intratumoral expression of ERα and in relevant models it has been

shown that such resistance can be reversed by the SERD fulvestrant.[23-25] Likewise in human tumor explants it has been shown that inhibition of MAPK or Src results in an increase in ERα protein.[23] Thus, dual or multiple pathway inhibition may be required to realize the full potential of SERDs or SERMs. Indeed, the recent results of the Paloma 3 clinical trial were very encouraging as it was reported that regimens in which the cdk4/6 inhibitor (palbociclib) and fulvestrant were combined demonstrated an impressive improvement in progression free survival (10 months) when compared to fulvestrant plus placebo in women with ER positive metastatic breast cancer. Similar studies of cdk/6 inhibitors in combination with the newer SERDs (GDC-0810) are expected. The results of a recently opened clinical trial of palbociclib with bazedoxifene (a SERM that significantly downregulates ERα expression) will also be important to the field.

Finally, it remains to be determined if all SERDs are the same. Currently, there are at least three chemical classes of SERDs either approved or in development: (a) steroids (fulvestrant), (b) acrylic acids (GW5638/GDC0810), and (c) others (OP-1094) **(Table 1)**. From what is known, thus far, it appears as if the mechanisms underlying the SERD activity of these different classes of compounds are not the same. [26, 27] Identification of the specific E2/E3 ubiquitin ligases responsible for the activity of these drugs and a determination of the relationship between the expression of these particular enzymes and efficacy may enable approaches to personalize SERD usage.

In conclusion, as evidenced by the studies presented in Lai et al, there has been considerable progress of late in developing orally bioavailable SERDs and it is likely that these will have a significant impact on the pharmacotherapy of breast cancer. Given that GDC-0810 and AZD9694 are already in clinical trials it is likely that the answers to some of the questions raised above will be answered in the relatively near future.

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References

1. Mayer EL. Targeting breast cancer with CDK inhibitors. Curr Oncol Rep. 2015; 17:443. [PubMed: 25716100]
2. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012; 366:520–9. [PubMed: 22149876]
3. Johnston SR. Endocrine manipulation in advanced breast cancer: recent advances with SERM therapies. Clin Cancer Res. 2001; 7:4376s–4387s. discussion 4411s-4412s. [PubMed: 11916228]
4. Deshmane V, Krishnamurthy S, Melemed AS, Peterson P, Buzdar AU. Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. J Clin Oncol. 2007; 25:4967–73. [PubMed: 17971595]
5. DeFriend DJ, Howell A, Nicholson RI, Anderson E, Dowsett M, Mansel RE, Blamey RW, Bundred NJ, Robertson JF, Saunders C, Baum M, Walton P, Sutcliffe F, Wakeling AE. Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. Cancer Res. 1994; 54:408–414. [PubMed: 8275477]

6. Robertson JFR. Fulvestrant (Faslodex)-How to make a good drug better. The Oncologist. 2007; 12:774–784. [PubMed: 17673609]

7. Lai A, Kahraman M, Govek S, Nagasawa J, Bonnefous C, Julien J, Douglas K, Sensintaffar J, Lu N, Lee KJ, Aparicio A, Kaufman J, Qian J, Shao G, Prudente R, Moon MJ, Joseph JD, Darimont B, Brigham D, Grillot K, Heyman R, Rix PJ, Hager JH, Smith ND. Identification of GDC-0810 (ARN-810), an orally bioavailable Selective Estrogen Receptor Degrader (SERD) that demonstrates robust activity in tamoxifen-resistant breast cancer xenografts. J Med Chem. 2015

8. McDonnell DP, Wardell SE. The molecular mechanisms underlying the pharmacological actions of ER modulators: implications for new drug discovery in breast cancer. Current opinion in pharmacology. 2010; 10:620–8. [PubMed: 20926342]

9. Gottardis MM, Robinson SP, Satyaswaroop PG, Jordan VC. Contrasting actions of tamoxifen on endometrial and breast tumor growth in the athymic mouse. Cancer Res. 1988; 48:812–815. [PubMed: 3338079]

10. Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, Carbone PP, DeMets DL. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. New Engl. J. Med. 1992; 326:852–856. [PubMed: 1542321]

11. Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer. 2009; 9:631–43. [PubMed: 19701242]

12. Norris JD, Paige LA, Christensen DJ, Chang C-Y, Huacani MR, Fan D, Hamilton PT, Fowlkes DM, McDonnell DP. Peptide antagonists of the human estrogen receptor. Science. 1999; 285:744–746. [PubMed: 10426998]

13. Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA, Greene GL. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell. 1998; 95:927–937. [PubMed: 9875847]

14. Connor CE, Norris JD, Broadwater G, Willson TM, Gottardis MM, Dewhirst MW, McDonnell DP. Circumventing tamoxifen resistance in breast cancers using antiestrogens that induce unique conformational changes in the estrogen receptor. Cancer research. 2001; 61:2917–22. [PubMed: 11306468]

15. Willson TM, Henke BR, Momtahen TM, Charifson PS, Batchelor KW, Lubahn DB, Moore LB, Oliver BB, Sauls HR, Triantafillou JA, Wolfe SG, Baer PG. 3-[4-(1,2-diphenylbut-1-enyl)phenyl]acrylic acid: A non-steroidal estrogen with functional selectivity for bone over uterus in rats. J. Med. Chem. 1994; 37:1550–1552. [PubMed: 8201587]

16. Wu Y-L, Yang X, Ren Z, McDonnell DP, Norris JD, Willson TM, Greene GL. Structural basis for an unexpected mode of SERM-mediated ER antagonism. Mol. Cell. 2005; 18:413–424. [PubMed: 15893725]

17. Schafer JM, Lee ES, Dardes RC, Bentrem D, O'Regan RM, De Los Reyes A, Jordan VC. Analysis of cross-resistance of the selective estrogen receptor modulators arzoxifene (LY353381) and LY117018 in tamoxifen-stimulated breast cancer xenografts. Clin Cancer Res. 2001; 7:2505–12. [PubMed: 11489833]

18. Masamura S, Santner SJ, Heitjan DF, Santen RJ. Estrogen deprivation causes estradiol hypersensitivity in human breast cancer cells. J. Clin. Endocrinol. Metab. 1995; 80:2918–2925. [PubMed: 7559875]

19. Jeselsohn R, Yelensky R, Buchwalter G, Frampton G, Meric-Bernstam F, Gonzalez-Angulo AM, Ferrer-Lozano J, Perez-Fidalgo JA, Cristofanilli M, Gomez H, Arteaga CL, Giltnane J, Balko JM, Cronin MT, Jarosz M, Sun J, Hawryluk M, Lipson D, Otto G, Ross JS, Dvir A, Soussan-Gutman L, Wolf I, Rubinek T, Gilmore L, Schnitt S, Come SE, Pusztai L, Stephens P, Brown M, Miller VA. Emergence of constitutively active estrogen receptor-alpha mutations in pretreated advanced estrogen receptor-positive breast cancer. Clin Cancer Res. 2014; 20:1757–67. [PubMed: 24398047]

20. Freedman RA, Anders CK. Treatment of Breast Cancer Brain Metastases. Curr Breast Cancer Rep. 2012; 4:1–9. [PubMed: 22754605]

21. Duchnowska R, Dziadziuszko R, Trojanowski T, Mandat T, Och W, Czartoryska-Arlukowicz B, Radecka B, Olszewski W, Szubstarski F, Kozlowski W, Jarosz B, Rogowski W, Kowalczyk A, Limon J, Biernat W, Jassem J, Polish Brain Metastasis, C. Conversion of epidermal growth factor

receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Res. 2012; 14:R119. [PubMed: 22898337]

22. Simpson ER. Sources of estrogen and their importance. J. Steroid Biochem. Mol. Biol. 2003; 86:225–230. [PubMed: 14623515]
23. Creighton CJ, Hilger AM, Murthy S, Rae JM, Chinnaiyan AM, El-Ashry D. Activation of mitogen-activated protein kinase in estrogen receptor alpha-positive breast cancer cells in vitro induces an in vivo molecular phenotype of estrogen receptor alpha-negative human breast tumors. Cancer Res. 2006; 66:3903–3911. [PubMed: 16585219]
24. Xia W, Bacus S, Hegde P, Husain I, Strum J, Liu L, Paulazzo G, Lyass L, Trusk P, Hill J, Harris J, Spector NL. A model of acquired autoresistance to a potent ErbB2 tyrosine kinase inhibitor and a therapeutic strategy to prevent its onset in breast cancer. Proc. Natl. Acad. Sci. USA. 2006; 103:7795–7800. [PubMed: 16682622]
25. Bosch A, Li Z, Bergamaschi A, Ellis H, Toska E, Prat A, Tao JJ, Spratt DE, Viola-Villegas NT, Castel P, Minuesa G, Morse N, Rodon J, Ibrahim Y, Cortes J, Perez-Garcia J, Galvan P, Grueso J, Guzman M, Katzenellenbogen JA, Kharas M, Lewis JS, Dickler M, Serra V, Rosen N, Chandarlapaty S, Scaltriti M, Baselga J. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. Sci Transl Med. 2015; 7:283ra51.
26. Wijayaratne AL, Nagel SC, Paige LA, Christensen DJ, Norris JD, Fowlkes DM, McDonnell DP. Comparative analyses of the mechanistic differences among antiestrogens. Endocrinology. 1999; 140:5828–5840. [PubMed: 10579349]
27. Wittmann BM, Sherk A, McDonnell DP. Definition of functionally important mechanistic differences among selective estrogen receptor down-regulators. Cancer research. 2007; 67:9549–60. [PubMed: 17909066]

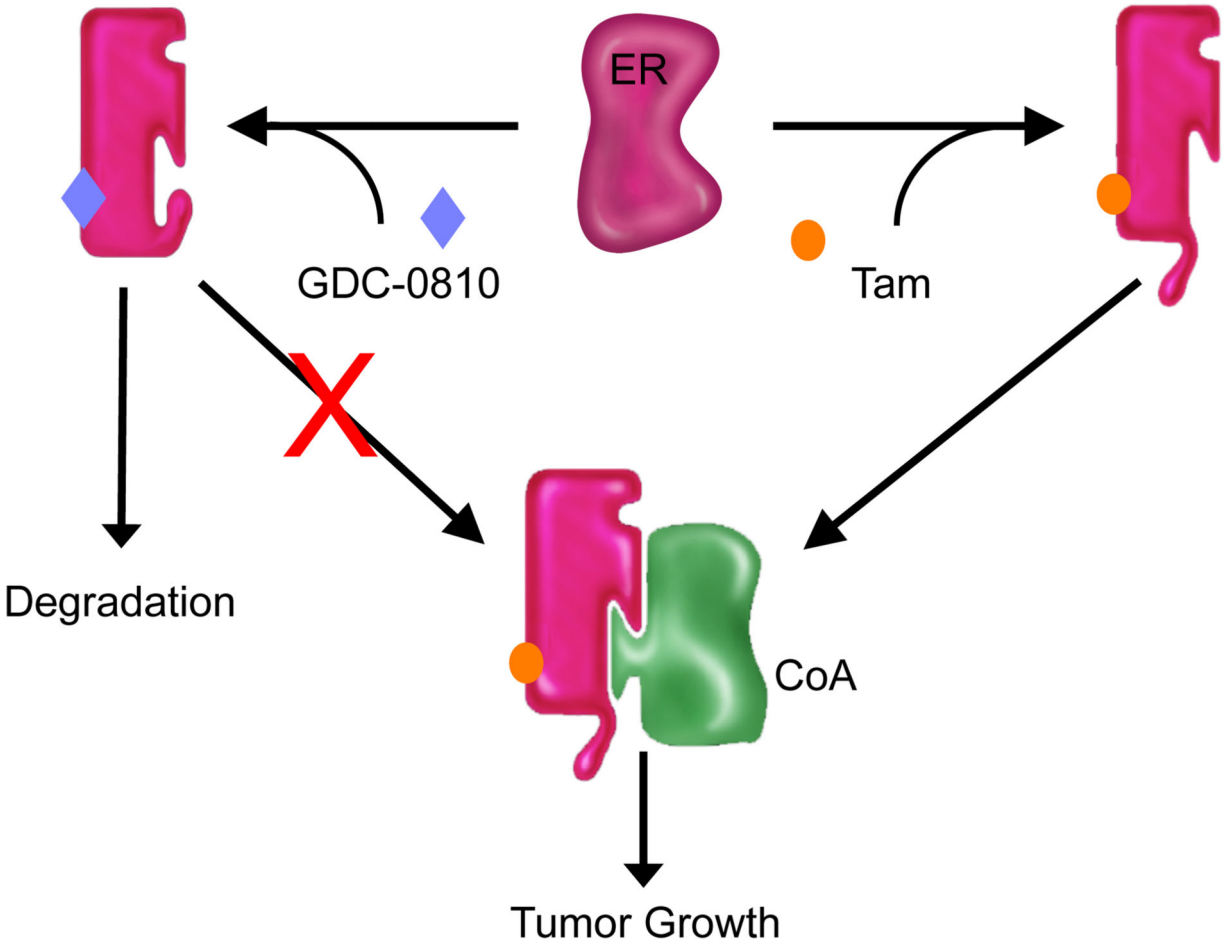

Figure 1. The molecular pharmacology of SERDs in the setting of tamoxifen resistance

Upon binding tamoxifen ERα undergoes a specific conformational change that enables the presentation of protein-protein interaction surfaces for which in tamoxifen sensitive cells there are no compatible coregulators. Thus, tamoxifen binding commits ER down a "non-productive" pathway, an activity that manifests as antagonism. It is proposed that chronic administration of tamoxifen, however, results in the selection of a subpopulation of cells that express a compatible coactivator (CoA). In this manner the pharmacology of tamoxifen "switches" from that of an antagonist to an agonist. SERDs, like GDC-0810, have activity in the setting of tamoxifen resistance as they (a) they function as high affinity competitive antagonists, (b) induce a conformational change that is incompatible with coregulator interactions and (c) target the receptor for proteasomal degradation.

Table 1

Structures of ER-modulators which display SERD activity in cellular and animal models of breast cancer