The First Targeted Therapy to Treat Cancer: The Tamoxifen Tale

Balkees Abderrahman and V. Craig Jordan

Abstract The chance discovery of a new group of medicines called nonsteroidal anti-estrogens opened the door to new opportunities in therapeutics. Ethamoxytriphetol (MER25) was the first. However, based on studies in rats and mice, initial hopes were that nonsteroidal anti-estrogens would be new "morning after pills." However, the discovery that clomiphene and tamoxifen induced ovulation in subfertile women would produce only a niche market in the 1960s. The treatment of metastatic breast cancer was an obvious choice as endocrine ablative surgery, i.e., oophorectomy, adrenalectomy, or hypophysectomy, was standard of care. Over a decade, in the 1970s, numerous nonsteroidal anti-estrogens were tested, but only tamoxifen went forward for the treatment of all stages of breast cancer, ductal carcinoma in situ, and male breast cancer and the reduction of risk for breast cancer in high-risk pre- and postmenopausal women.

Keywords Nonsteroidal anti-estrogens · Nafoxidine · Clomiphene · Tamoxifen · Estrogen receptor · Breast cancer therapy and prevention

1 Introduction

In 1958, Lerner and coworkers [1] described the anti-estrogenic properties of the first nonsteroidal anti-estrogen ethamoxytriphetol (MER25) (Fig. 1). The compound was discovered by accident. Lerner was scanning the structures of compounds that were being tested in the cardiovascular program at William S. Merrell, in Cincinnati. He was the new young leader of their synthetic estrogen program. Lerner noted that MER25 had a structure similar to the triphenylethylene estrogens [2] used clinically. He asked to test MER25 as an estrogen.

Unexpectedly, MER25 was found to be an anti-estrogen in all species tested and had little or no estrogenic actions at estrogen target tissues [1]. Although numerous

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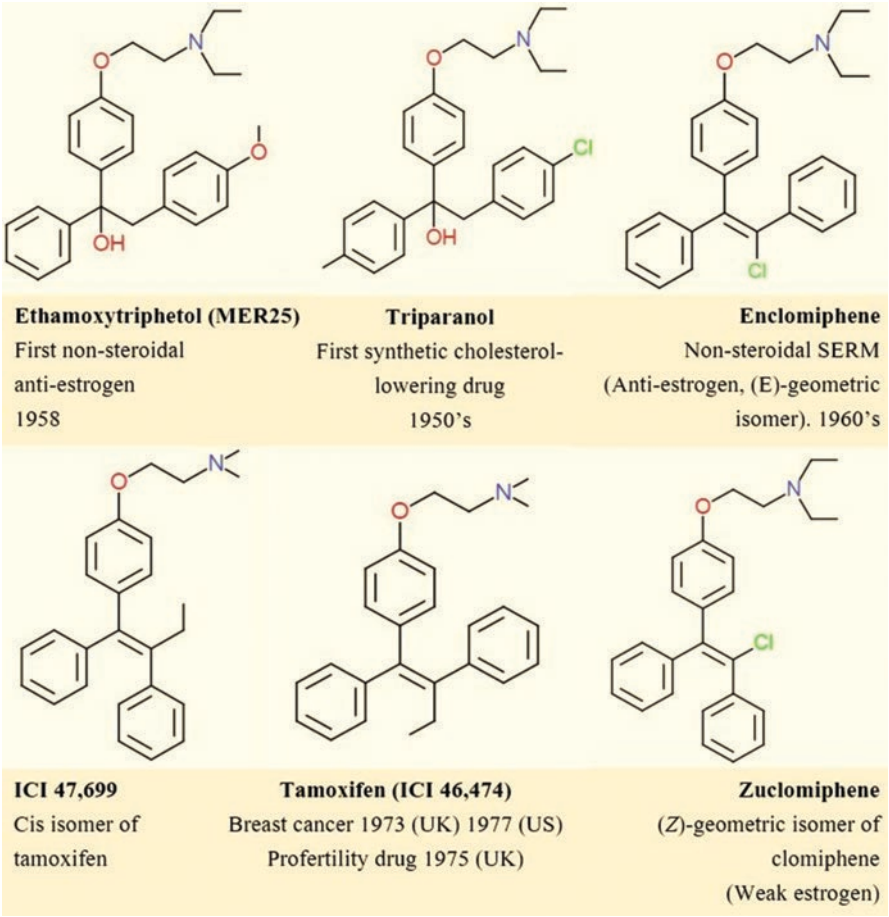


Fig. 1 The structures of early nonsteroidal anti-estrogens and in the case of clomiphene the separated geometric isomers and tamoxifen's estrogenic *cis*-isomer. Triparanol, a cholesterol lowering drug used clinically, is included to demonstrate structural similarities with the nonsteroidal anti-estrogens

applications were suggested for an anti-estrogen in therapeutics [2], it was the finding [3] that MER25 was an antifertility agent in animals that seized the enthusiasm of the pharmaceutical industry. This was because the oral contraceptive, which had recently been successfully tested in clinical trial, had revolutionized the approach to therapeutics. For the first time, individuals were being treated who had no disease. Naturally, Merrell moved forward with MER25, but it was found to be too toxic and of low potency for human use. MER25, however, was valuable as a research tool to study the mechanism of action of estrogen at estrogen target tissues. Dr. Elwood Jensen was the first to show that pretreatment of immature rats with MER25

prevented the uptake of administered [^{3}H] estradiol in the immature rat uterus (noted in the discussion of Emmens, Cox, and Martin "anti-estrogens" [4]).

Lerner was involved in Merrell's second anti-estrogen MRL41 or clomiphene [5] (Fig. 1). However, clomiphene is a mixture of *cis*- and *trans*-geometric isomers of a substituted triphenylethylene. Antifertility activity was noted in animals [5], but clinical testing demonstrated the induction of ovulation in subfertile women [6].

Clomiphene is only used in short 5-day courses for the induction of ovulation in subfertile women. This is because clomiphene interrupts cholesterol metabolism and increases the circulating levels of desmosterol. Merrell did not continue clinical testing for indications like breast cancer therapy because of the known link between high circulating levels of desmosterol and early cataract formation [7].

Earlier in the 1950s, Merrell had marketed a medicine called triparanol (Fig. 1) for individuals who needed to reduce their high circulating levels of cholesterol. Triparanol caused an increase in cataracts in young patients [8], and this was linked to increases in circulating desmosterol levels [7]. This litigious history mandated that Merrell would not market any agent that increased circulating desmosterol. Nevertheless, scientist at Merrell separated the *cis*- and *trans*-isomers of clomiphene [9] to determine whether they could improve the toxicology of clomiphene (Fig. 1). Unfortunately, they mislabeled the isomers: the trans-isomer was identified as an estrogen with no anti-estrogen actions, and the cis-isomer was misidentified as the anti-estrogenic isomer. None of this would have mattered had not other pharmaceutical companies rigorously investigated the structure function relationships of nonsteroidal anti-estrogens. The goal was to find the clinical use for a safe anti-estrogen.

The UpJohn Company mounted a huge investigation of the structure function relationships of fixed ring naphthalene-based antifertility agents. ICI Pharmaceuticals Division (now AstraZeneca) would follow but with a study of the antifertility properties of the separated isomers of substituted triphenylethylenes [10] (Fig. 1).

Nafoxidine derivatives established structure function relationships for the required position of the "anti-estrogenic side chain." Figure 2 summarizes the extensive structure functions relationship studies conducted on the 3-methoxy naphthalene core as experimental antifertility agents. The substitution on the p-phenyl ethoxyamine side chain is critical for antifertility activity in laboratory animals [11]. Similarly, the length of the *para*-substituted amino side chain of nafoxidine is critical for anti-estrogenic activity in animals [11, 12]. Indeed, Lednicer [11] suggested that *a basic group, at a given position in space is required to obtain a molecule with estrogen antagonist activity*. All compounds with a short side chain are estrogens. Indeed, the substitution of two methyl groups *ortho* to the anti-estrogenic side chain of MER25 [13] and tamoxifen [14] completely reduces anti-estrogenic actions in vivo. The movement of the anti-estrogenic side chain is restricted and cannot rotate and position itself correctly in the estrogen receptor (ER) binding domain.

It is important to appreciate the scale of these extensive animal studies on the antifertility properties of test compounds. In the early 1960s, studies to discover compounds of clinical relevance were only performed in vivo with an antifertility or

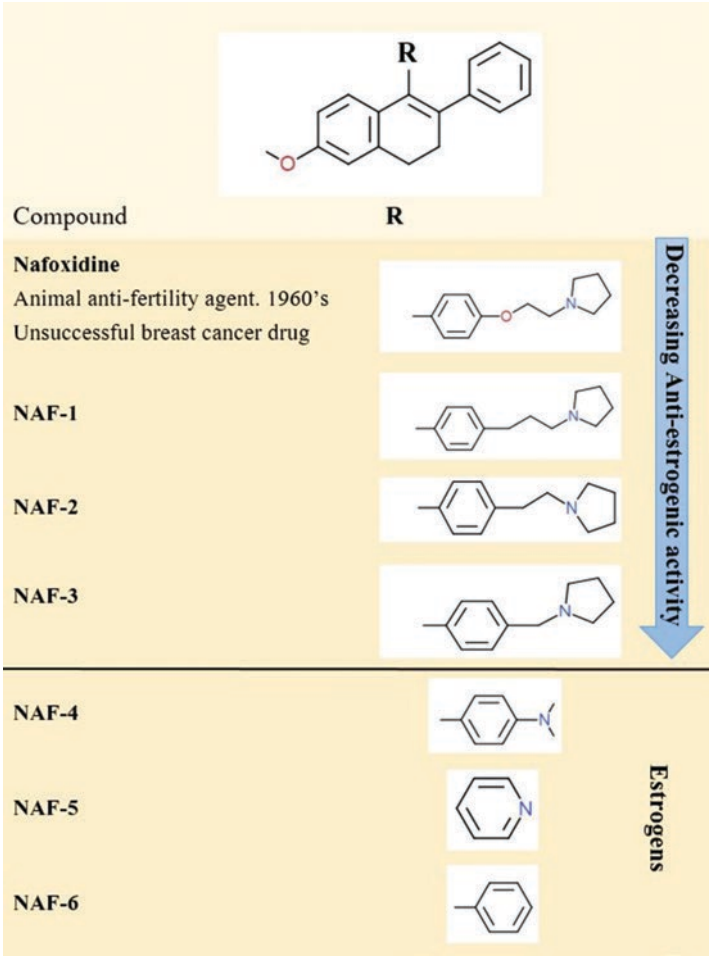


Fig. 2 The critical importance of the anti-estrogenic side chain R of nafoxidine to program anti-estrogenic activity of the steroidal anti-estrogen nafoxidine

anti-estrogenic endpoint in rats or mice. There was no reference to mechanisms of action via the ER as the work of Jensen [15, 16] and Gorski [17, 18] was only just starting and the notion of an ER was not universally accepted as the mechanism of estrogen action. Only the pharmacology of anti-estrogens would verify receptor status for the ER as a mediator of female physiology.

Nafoxidine entered clinical trials for the treatment of metastatic breast cancer (MBC) [19], but the ubiquitous side effects of photophobia and skin rashes caused industry to abandon clinical studies. The husband and wife Katzenellenbogen team pursued an analog U23,469 as a tool to understand the metabolic activation of nafoxidine derivatives through demethylation [20]. In addition, the change in the alkylaminoethoxy side chain was thought to reduce side effects noted with

nafoxidine. Despite all of the setbacks with nafoxidine, this molecular scaffold proved to be important for medicinal chemist to create lasofoxifene [21], 30 years later. This molecule will be discussed in the companion chapter, "A Novel Strategy to Improve Women's Health: Selective Estrogen Receptor Modulators" (SERMs). The clinical pharmacology of lasofoxifene exhibits all the properties predicted for SERMs in the original vision statement [2]. The new clinical strategy was based on the early clinical studies with tamoxifen and laboratory studies with keoxifene which would subsequently be reinvented as raloxifene.

2 Tamoxifen Moves Forward Alone but with a Strategic Plan

Imperial Chemical Industry (ICI), now AstraZeneca, has a long history in the synthesis of novel nonsteroidal estrogens. The first chemical therapy for the successful treatment of any cancer was the use of high-dose synthetic estrogens for the treatment of MBC [22]. A response rate of 30% was observed in patients more than 5 years postmenopause [23]. The synthetic estrogens (Fig. 3) were synthesized by ICI Pharmaceuticals Division. Dr. Arthur Walpole, who would become the head of the fertility control program in the new facilities at Alderley Park [26], had an interest in determining which tumors would respond to high-dose estrogen therapy [24]. He was unsuccessful, but the clinical collaboration at the Christie Hospital in Manchester would be critical for the advance of ICI46,474 to become tamoxifen [27].

Harper and Walpole [10] first described the unusual pharmacological properties of the *cis*- and *trans*-isomers of a substituted triphenylethylene. ICI47,699 (*cis*) was estrogenic, but ICI46,474 (*trans*) was anti-estrogen in rats, but both compounds were estrogens in mouse vaginal cornification and uterine weight tests (Fig. 1). Synthesis, isomer separation, and X-ray crystallography proved isomer structure related to biology [28, 29]. The controversy concerning the reverse pharmacology [30] of the separated clomiphene isomers was settled appropriately by the Merrell company changing their isomer names to enclomiphene (*trans*) and zuclomiphene (*cis*) after the German entgegen (opposite) and zusammen (together) referring to the unsubstituted phenyls at the double bond of the ethylene scaffold (Fig. 1).

All laboratory efforts at Alderley Park focused entirely on the antifertility properties of ICI46,474 as a postcoital contraceptive [31–36]. Clinical testing, however, demonstrated that tamoxifen induced ovulation in subfertile women [37, 38]. Tamoxifen is approved for the induction of ovulations in some countries. The details of the design and development of a clinical plan for tamoxifen are documented in the personal postscript. The clinical strategy [39, 40] that was stated and translated was the following: (1) only use tamoxifen to treat ER-positive breast cancer patients, (2) use it long term (forever but starting with 5 years), and (3) tamoxifen can prevent mammary cancer in rats and (subsequently) in mice [41]. Chemoprevention was a possibility for women at high risk. However, very little was known about the clinical pharmacology of tamoxifen during long-term therapy, and there was no information about the metabolism and pharmacology of tamoxifen metabolites.

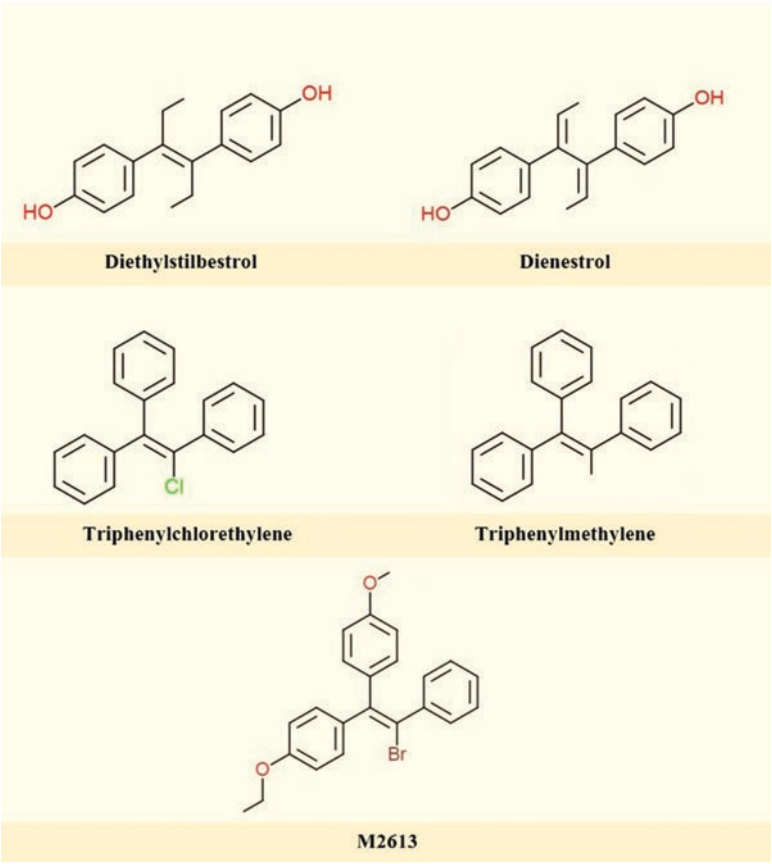


Fig. 3 Formulae of nonsteroidal estrogens used by Dr. A. L. Walpole in clinical studies with Edith Paterson at the Christie Hospital for the treatment of advanced breast cancer [24]. The compounds originally used by Haddow and coworkers (diethylstilbestrol, triphenylchlorethylene, triphenylmethylethylene) [25] are illustrated for comparison

An examination of the metabolism of tamoxifen and the structure function relationships of nonsteroidal anti-estrogens will be addressed first, followed by a summary of the clinical advance with tamoxifen. Both aspects of the pharmacology of tamoxifen combined advanced the discovery of a new group of medicine referred to as SERMs.

3 The Metabolism of Tamoxifen

The original investigation of the metabolism of tamoxifen was conducted at Alderley Park [26] and published in 1973 [42, 43]. Administration of ^{14}C-labeled tamoxifen to rats, mice, monkeys, and dog demonstrated that the major route of excretion was

via the feces. Dog and rat studies demonstrated that over 50% of the radioactivity was excreted via the bile duct and 70% was reabsorbed. There was enterohepatic recirculation. The hydroxylated metabolites were glucuronidated prior to biliary excretion, but there was no information about the biological properties of the three metabolites (Fig. 4) [42, 43]. The hydroxylated metabolites of tamoxifen were 4-hydroxytamoxifen and 3,4-dihydroxytamoxifen, and in the dog, a phenolic metabolite of tamoxifen formed by cutting off the dimethylaminoethyl side chain at the ether link to its phenyl group (metabolite E). A study in four women identified 4-hydroxytamoxifen as the primary metabolite [43]. However, the original technique of thin layer chromatography used to identify 4-hydroxytamoxifen was flawed [44], and N-desmethyltamoxifen was subsequently identified as the major metabolite of tamoxifen [45]. The side chain of tamoxifen was further metabolized (Fig. 5) to N-didesmethyltamoxifen (metabolite Z) [46] and deaminated to metabolite Y, a glycol derivative of tamoxifen [47, 48]. The next surprise, at the end of the 1980s, was the identification of 4-hydroxy-N-desmethyltamoxifen [49, 50]. The current status of tamoxifen metabolism is noted in Fig. 5; there is now evidence that two estrogenic metabolites of tamoxifen occur: metabolite E formed from tamoxifen and bisphenol formed from 4-hydroxytamoxifen [51].

The evaluation of the estrogenic and anti-estrogenic actions of the metabolites of tamoxifen provided a breakthrough for understanding estrogen and anti-estrogen

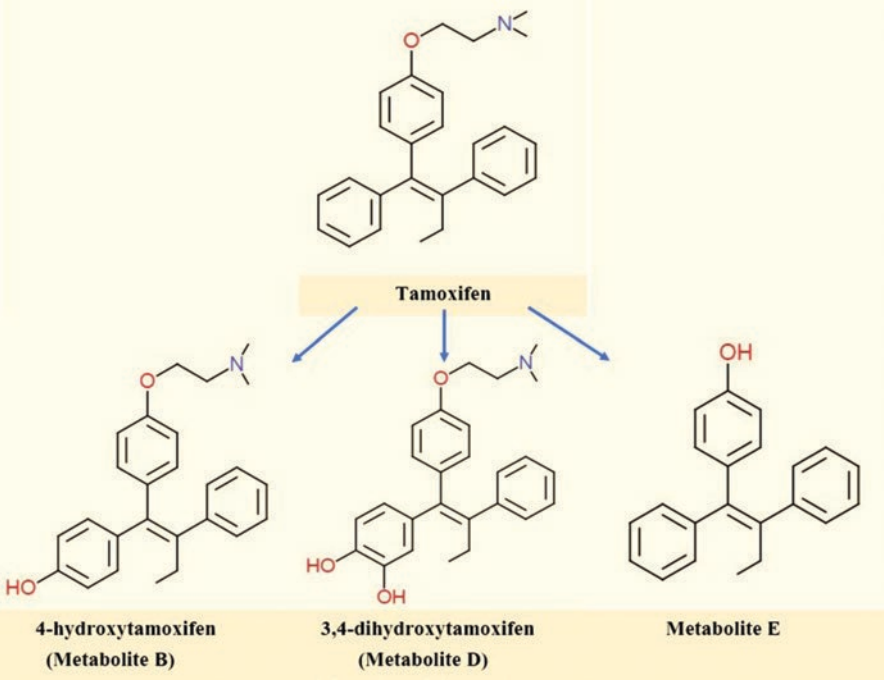


Fig. 4 The original hydroxylated metabolites of tamoxifen noted in animals [42]

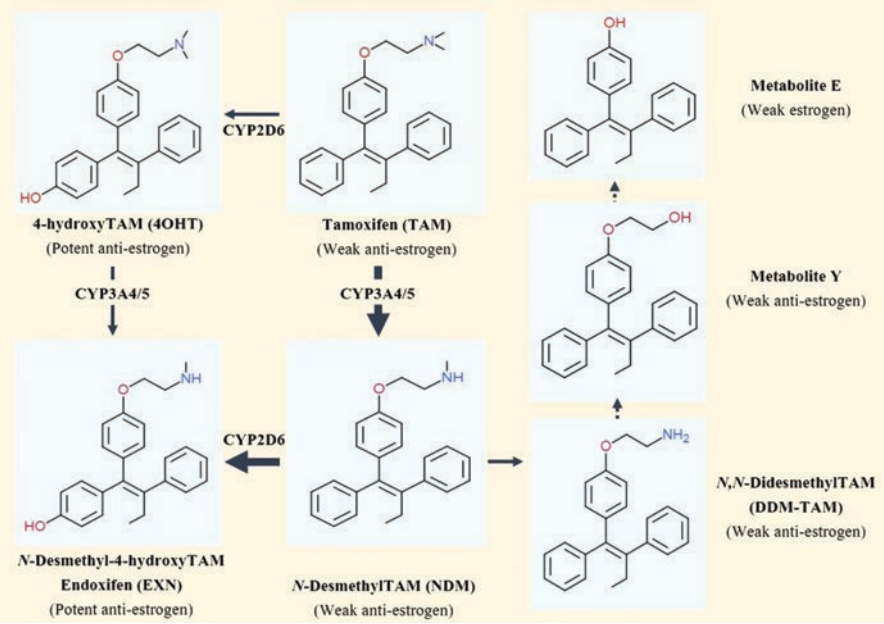


Fig. 5 The metabolic activation of tamoxifen to phenolic metabolites that have a high binding activity for the human estrogen receptor. Both 4-hydroxytamoxifen and endoxifen are potent anti-estrogens in vitro

action. Knowledge of the metabolites were the backbone structure to initiate structure-activity relationship studies investigated to develop new medicines called SERMs. Overall, these early investigations and clarifications provided an understanding of the molecular mechanisms action of anti-estrogens.

Although tamoxifen possesses weak anti-estrogenic action, the molecule is activated by 4-hydroxylation to either 4-hydroxytamoxifen [52, 53] or the activation of N-desmethyltamoxifen to 4-hydroxy-N-desmethyltamoxifen or endoxifen. Endoxifen is created by the enzyme CYP2D6 [54], and there has been much interest in linking the genomic mutation of the *CYP2D6* with the response of ER-positive breast cancer to tamoxifen treatment. Recently endoxifen has been reinvented as a second line of cancer therapy in MBC following the failure of AI therapy [55, 56].

4 Molecular Pharmacology of the Tamoxifen ER Complex

The first model used to study estrogen and anti-estrogen action in vitro was the MCF7 breast cancer cell line [57]. However, the results were perplexing. Despite the use of rigorously prepared charcoal-stripped serum, MCF7 cells grew with or without added estrogen [58]. Tamoxifen treatment alone caused a decline in cell growth that could be reversed by estrogen. Indeed, a comparison of MCF7 cells

in vitro with MCF7 cell inoculated into ovariectomized athymic mice and treated with estrogen demonstrated estrogen-stimulated tumor growth in vivo but not in vitro [59]. This observation led to the idea that estrogen was stimulating a second messenger molecule in the athymic mouse that actually caused tumors to grow. A decade later the Katzenellenbogens discovered [60–62] that culture media indicator (phenol red) contained an estrogenic impurity and MCF7 cells were already growth-stimulated before adding estradiol. Their discovery opened the door to molecular studies of estrogen/anti-estrogen action in breast cancer. Nevertheless, studies in vitro of estrogen-stimulated prolactin synthesis [63], in disrupted anterior pituitary gland cells from immature mice, set the scene to understand estrogen/anti-estrogen action at the level of the ER complex. Cancer cell sensitivity to estrogen as a growth stimulus is extraordinarily low in the range of 10^{-12} M for estradiol. Protein synthesis is regulated at 10–100 logs higher concentration.

5 The Molecular Modulation of Prolactin Synthesis via the ER

Studies in vitro avoid the complications of metabolism in vivo and identify the actions of each metabolite or compound as an estrogen, anti-estrogen, or partial agonist. Studies, in vitro with tamoxifen, its metabolites, and tamoxifen derivatives that could not be metabolically activated to high affinity for 4-hydroxytamoxifen, established a direct and reversible inhibition of estrogen-stimulated prolactin synthesis via the ER [64]. Additionally, ER binding ligands were predictably classified into agonist, partial agonist, and antagonist based upon structure [65–68]. A hypothetical pharmacological model (Fig. 6) of the ER binding domain/ligand interaction could predictably convert an agonist ligand to antagonist based on the length and positioning of the bulky anti-estrogenic side chain of triphenylethylene derivatives [66, 70].

A parallel collaborative study, using both monoclonal antibodies and a goat polyclonal antibody to the human ER, provided valuable supporting evidence for the molecular models developed by the modulation of prolactin synthesis. The [^{3}H] labeled 4-hydroxytamoxifen and [^{3}H] estradiol were compared and contrasted in human breast cancer and rat pituitary tumor ER [71, 72]. The monoclonal antibodies did not detect differences in the ligand ER complex [73]. By contrast, preincubation of the polyclonal antibody with human breast or rat pituitary tumor ER prevented [^{3}H] estradiol binding, but [^{3}H] 4-hydroxytamoxifen binding was unaffected by preincubation. A model was proposed, whereby estradiol binds and is locked into the ER complex with the ligand sealed within the protein complex. By contrast, the anti-estrogen binds within the ligand-binding domain, but the bulky anti-estrogenic side chain ensures that the ligand remains wedged within the receptor (Fig. 7). The mechanism was referred [74] to as “the crocodile model”: planar estradiol is sealed within the jaws of the crocodile, but 4-hydroxytamoxifen binds

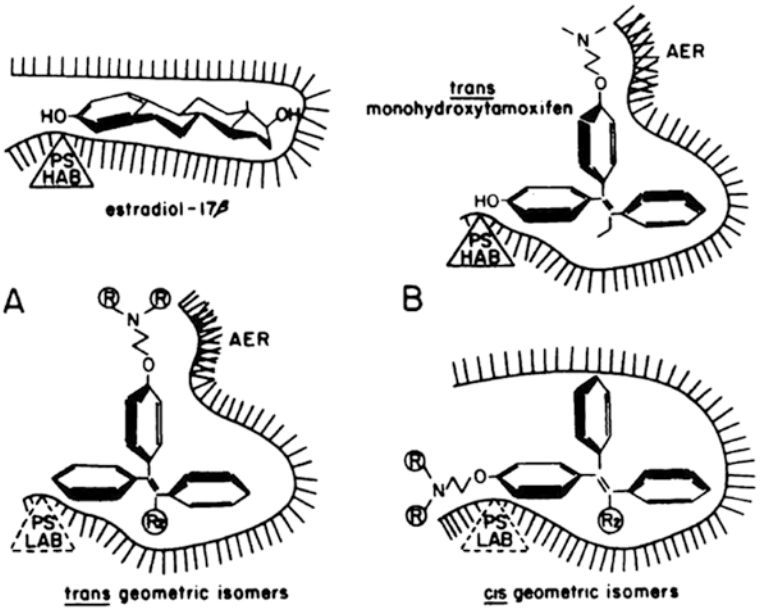


Fig. 6 Hypothetical models for estrogenic and anti-estrogenic ligands binding to the estrogen receptor. Estradiol-17β is anchored at a phenolic site (PS) with high affinity binding (HAB). *Trans*-monohydroxytamoxifen has the same high affinity binding, but this anti-estrogenic ligand binds to the receptor site so that the alkylaminoethoxy side chain can interact with a hypothetical anti-estrogen region (AER) on the protein. Compounds without a phenolic hydroxyl have low affinity binding (LAB). The *trans*- and *cis*-geometric isomers refer to (**a**) tamoxifen (R1 = CH_3, R_2, = C_2H_5) and enclomiphene (R = C_2H_5, R_2 = C1) and (**b**) ICI 47,699 (R = CH_3, R = C_2H_5) and zuclomiphene (R = C_2H_5, R_2 = C1). Reproduced with permission from [69]

with high affinity, but the bulky side chain is like "a stick in the jaws of the crocodile" to prevent closure. Indeed, Lieberman and coworkers [70] (Fig. 6) predicted that there was an "anti-estrogenic region" that interacts with the dimethylalkylaminoethoxyphenyl side chain of 4-hydroxytamoxifen. This "anti-estrogenic region" was subsequently identified as amino acid 351 [75] (Fig. 8), evaluated in molecular pharmacology studies [77–81], and physically identified by comparing and contrasting the molecular fit of 4-hydroxytamoxifen and raloxifene by X-ray crystallography [82, 83]. Amino acid asp351 is important for interaction with the anti-estrogenic side chain of SERMs to modulate the estrogen-like actions of the SERM-ER complex. Extensive studies of the relationship of the nitrogen-containing side chain of SERMs with different amino acids at asp351 are informative [77–81]. This interaction is important to prevent helix 12 appropriately sealing the ligand within the ER complex. Modulation with agonists, partial agonists, and antagonist creates the range of SERM/agonist/antagonist action. Indeed, the essential nature of this well-studied amino acid asp351 [77–81] has recently been identified as a significant form of acquired resistance in aromatase inhibitor therapy. Amino acid

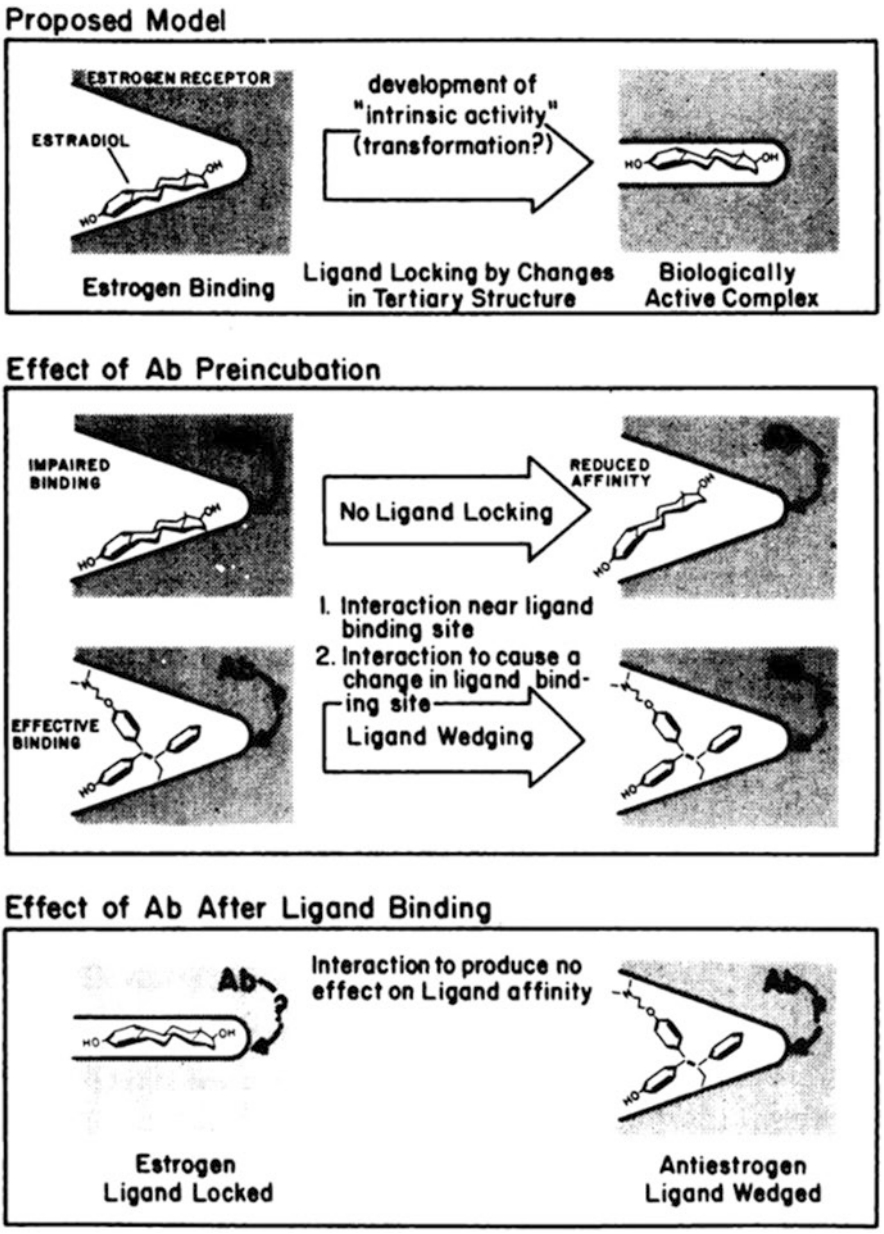


Fig. 7 Effect of goat polyclonal antibody (Ab) on the binding of estradiol and monohydroxytamoxifen to the ligand-binding site on the ER. Reproduced with permission from [71]

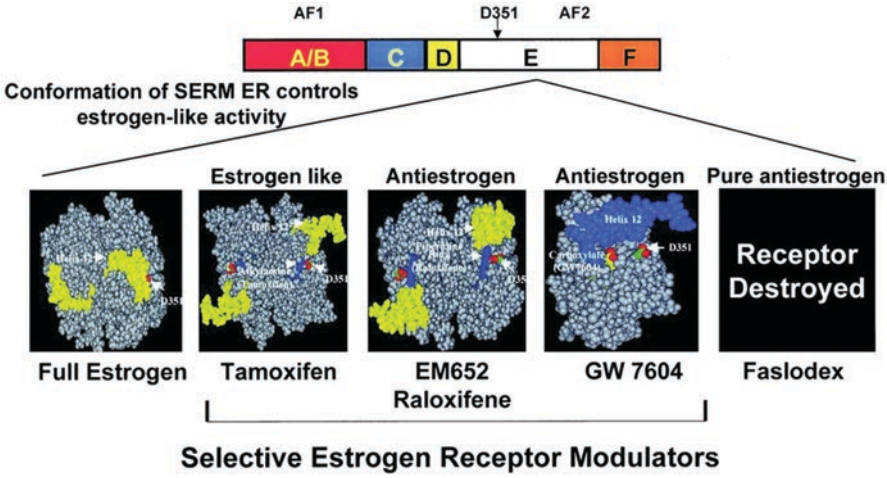


Fig. 8 The modulation of the ERα complex by interaction of the anti-estrogenic side chain of SERMs with surface amino acid D351. Data adapted from X-ray crystallography and the biology of complexes. Reproduced with permission from [76]

asp351 seals the unoccupied ER by binding to mutant amino acids at 537, 538 in helix 12 [84]. This unoccupied complex stimulates tumor growth.

The insight from Lednicer [11], some 50 years ago, is worth restating "a basic group, at a given position in space, is required to obtain a molecule with estrogen antagonist activity." The aforementioned events illustrate the continuum of research into ER-regulated events that traveled to a successful conclusion from (1) medicinal chemistry applied to define anti-estrogen action in vivo [11, 12, 85], (2) the discovery of a mutant amino acid asp351tyr in a natural model of drug resistance to tamoxifen in breast cancer [75, 77] that modulates estrogenic/anti-estrogenic action of the SERM-ER complex via a conversation of amino acids 351 with the SERM side chain [77–81], (3) the actual identification and proof of the "crocodile model" of estrogen/anti-estrogen side chain interacting with amino acid 351 revealed by X-ray crystallography (Fig. 8) (4) to the present with the autostimulation of AI-resistant breast cancer recurrence with mutant ER at amino acids 537/538 closing the empty ER with helix 12 at amino acid 351 [84].

6 Acquired Resistance to Tamoxifen, Clinical Endocrinology, and Long-Term Clinical Pharmacology

The use of models to determine mechanisms of tamoxifen action provides an insight into tamoxifen metabolism in various animal species and patients [86, 87]. The proposal, in the 1970s, to deploy long-term, i.e., 5 years or indefinite, adjuvant tamoxifen therapy, mandated an evaluation of tamoxifen treatment in patients over

time [88]. One concern, based on studies of acquired resistance to tamoxifen in athymic mice [89], was that long-term therapy might encourage the induction of metabolic pathways that produced estrogenic metabolites to simulate tumor growth. Tamoxifen was known to have a species-specific pharmacology, i.e., tamoxifen is an estrogen in mice [10], an anti-estrogen with partial estrogen-like properties in rats [31], and anti-estrogenic properties in chickens [90].

A standard model to study the actions of tamoxifen in vivo was the athymic mouse inoculated with breast cancer cells [57]. Continuous tamoxifen treatment of athymic mice transplanted with MCF-7 breast tumors, eventually results, demonstrates that tamoxifen cannot prevent breast cancer growth during a year of tamoxifen treatment [91]. This was important. One possibility was hormone-independent growth during tamoxifen treatment. Acquired resistance to treatment would then occur if the mouse model had amplification of metabolic enzymes that convert tamoxifen to high levels of estrogenic metabolites. The issue was clarified when tamoxifen-treated tumors were retransplanted tumors into a fresh generation of athymic mice. The discovery that tumors grew because of either tamoxifen or low-dose estrogen, not despite tamoxifen treatment, was unique. Molecular mechanisms have subsequently been deciphered [92, 93] and are summarized in Fig. 9. Additionally, studies [94] were conducted in athymic rats, where the pharmacology of tamoxifen is predominantly anti-estrogenic. Tamoxifen-stimulated tumor growth occurred in athymic rats. Therefore, it was the direct effect of the tamoxifen on the tumor rather than the host that was important.

These studies, and the successful testing of the first selective ER disrupter [95] SERD ICI 164,384 in the model of acquired resistance to tamoxifen, led to the development of fulvestrant [96] and the clinical evaluation of second-line treatments following the development of acquired tamoxifen resistance in MBC. Clinical trials, a decade later, demonstrated that either an aromatase inhibitor (anastrozole) or fulvestrant was equally effective second-line treatments [97, 98]. Tamoxifen-stimulated tumor growth has been demonstrated with a withdrawal response in the clinic [99].

Tamoxifen acts as an anti-estrogen to interfere with the hypothalamo-pituitary-ovarian access in premenopausal patients. There is an increase in ovarian secretion of estradiol and its metabolites [100]. Ovulation is triggered as evidenced by rises in progesterone secretion [101]. In postmenopausal patients, there are partial decreases in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Additionally, there are increases in antithrombin III and sex hormone binding globulin as an indication of the estrogen-like activity of tamoxifen and its metabolites [102]. At this point, it was important to establish whether the induction of tamoxifen-metabolizing enzymes occurs during long-term adjuvant therapy. Patients were monitored for up to 10 years, but no estrogenic metabolites were observed [88]. Results demonstrated stability for tamoxifen and its metabolites over this time period.

In the final sections, the clinical applications of tamoxifen will be summarized. Tamoxifen pioneered long-term anti-estrogen therapy for breast cancer. Additionally tamoxifen was successfully tested as a chemopreventative in high-risk pre- and postmenopausal women to reduce the incidence of breast cancer.

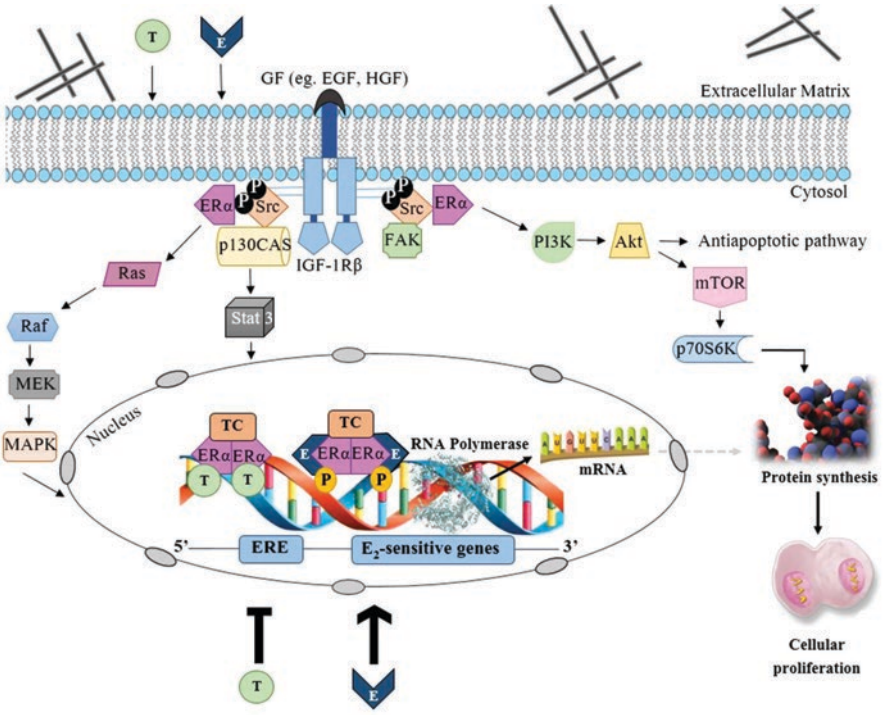


Fig. 9 Genomic and nongenomic signal transduction pathways in tamoxifen-resistant model. E_2 and TAM exert differential functions on nuclear ER. E_2 activates classical ER-target genes, but TAM acts to block gene activation. Both E_2 and TAM increase the nongenomic activity of ER through membrane-associated molecules such as c-Src, IGF-1Rβ, and FAK to enhance downstream signaling cascades. *IGF-1Rβ* insulin-like growth factor-1 receptor beta, *FAK* focal adhesion kinase, *c-Src* proto-oncogene tyrosine-protein kinase, *T* tamoxifen, *E* estrogen, *ERE* estrogen response element, *TC* transcription complex, *GF* growth factor, *MAPK* mitogen-activated protein kinase, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase

7 Long-Term Adjuvant Tamoxifen Therapy: The Prelude to Prevention

The initial testing of adjuvant tamoxifen therapy was cautious with a duration of 1 or 2 years [103]. This cautious approach, by the clinical community, was based upon their knowledge that tamoxifen was only effective for the treatment of MBC in 30% of patients for 2–3 years. However, the effectiveness of adjuvant tamoxifen therapy was based upon the fact that tamoxifen was preventing the estrogen-stimulated growth of micrometastatic disease and not the high tumor burden and mutational plasticity of MBC. The paradox with increases in survival with adjuvant tamoxifen was that tamoxifen is not a cytotoxic therapy. Clinical trials demonstrated long-term benefit following long-term adjuvant tamoxifen therapy [104, 105]. This is referred to as "the carryover effect." To explain decreases in recurrences and

mortality, after tamoxifen therapy stops, it is proposed that tamoxifen exerts continuous selection pressure on ER-positive populations of breast cancer cells which become resistant and ultimately sensitive to estrogen to initiate apoptosis [106].

There was initial caution about advancing adjuvant tamoxifen therapy beyond 5 years. This decision was made by building extension upon results from the 5-year NSABP node-negative trial B14 [107]. The new trial design was to compare and contrast women with node-negative disease who received either 5 years of tamoxifen or 10 years of tamoxifen [108]. The results demonstrated that patients receiving 10 years of tamoxifen had a higher increase in side effects but no therapeutic benefit was noted.

The EBCTCG lead the way with extrapolation of the benefits of tamoxifen. A recent evaluation of 15 years of follow-up of the efficacy of 5 years of adjuvant tamoxifen therapy demonstrates that despite the "carryover effect," recurrences occur relentlessly. These recurrences are predictable, with more recurrences occurring for patients that had a large primary tumor and large numbers of lymph nodes involved [109]. This begs the question: Is longer going to be better than shorter adjuvant therapy if 5 years is extended to 10 years of tamoxifen treatment?

Initial analysis of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial demonstrates both a decrease in recurrences for longer tamoxifen treatment and mortality decreases between 5 and 10 years of tamoxifen. However, the effect on mortality is only evident in the 5 years after 10 years of tamoxifen is completed [110]. A similar trial referred to as adjuvant Tamoxifen Treatment offers more (aTTom) has only been reported in abstract form. Nevertheless, data has been pooled [111] for ATLAS and aTTom demonstrating high significance for longer against shorter in recurrence and decreases in mortality. Nevertheless, it is important to ensure that strategies are devised to identify and treat only those patients at high risk of recurrence. It should not be forgotten that the rules of acquired resistance to tamoxifen treatment are relentless and consistent with all antihormone therapies. Rather than continuing adjuvant tamoxifen, in the words of author Basil A. Stoll "as a mindless exercise" [112], we need to develop an algorithm for who to treat and for how long.

The change in clinical care with a cheap and proven adjuvant treatment strategy for ER-positive breast cancer naturally caused an interest in the prevention of breast cancer in women at high risk. Three critical pieces of information all indicated that tamoxifen could reduce the risk of developing primary breast cancer. (1) Animal models demonstrated that tamoxifen could prevent chemical carcinogenesis in rats and spontaneous mammary carcinogenesis in high [113]- risk strains of mice [41]. (2) Tamoxifen prevented contralateral breast cancer during adjuvant therapy administered to prevent recurrence after the first breast cancer had been removed surgically [114]. (3) Clinical trials demonstrated the safety of tamoxifen during the treatment of node-negative breast cancer. There is only a 15–20% recurrence rate for node-negative ER-positive breast cancer, so the majority of patients treated in trials remain cancer-free for decades. In effect, these node-negative clinical trials acted as an evaluation of tamoxifen in women without cancer.

8 The Chemoprevention of Breast Cancer: A Flawed Strategy

The prevention of breast cancer in women is not a new idea. Professor Antoine Lacassagne stated at the American Association for Cancer Research in 1936 [115]:

> "If one accepts the consideration of adenocarcinoma of the breast as the consequence of special hereditary sensibility to the proliferative actions of estrone, one is led to imagine a therapeutic preventive for subjects predisposed by their heredity to this cancer. It would consist-perhaps in the very near future when the knowledge and use of hormones will be better understood – in the suitable use of a hormone antagonist or excretory, to prevent the stagnation of estrone in the ducts of the breast."

Some 50 years later, it was possible to consider chemoprevention as a realistic clinical opportunity. Dr. Trevor Powels took the first bold step at the Royal Marsden Hospital to initiate a pilot study of tamoxifen in women with known risk factors for breast cancer. The results of the pilot study, published in 1989 [116], justified the strategy based on two facts: (1) tamoxifen prevents rat mammary carcinogenesis [113]. (2) Short-term (2 years) adjuvant tamoxifen treatment for breast cancer caused a decrease in contralateral breast cancer [116].

Four large randomized clinical trials were initiated during the 1990s: (1) the Royal Marsden Study, (2) the NSABP P-1 Study, (3) the Italian Study, and (4) the International Breast Cancer Intervention Study (IBIS). The studies as a whole can be summarized (Table 1). The NSABP P-1 trial [117] demonstrated an approximate 50% decrease in breast cancer incidence for both pre- and postmenopausal high-risk women. There were no significant reductions in breast cancer incidence in the Italian study [118], but this was to be expected as the women were of normal risk and there was an added complication of allowing women to take hormone replacement therapy.

The overall value of chemoprevention with tamoxifen is limited. The public health strategy failed for two main reasons: (1) a thousand high-risk women need to

Table 1 Comparison of the tamoxifen randomized chemoprevention trials

Characteristics	Royal Marsden	NSABP	Italian	IBIS
Patient population	2471	13,388	5408	7152
Women/years of follow-up	12,355	46,856	5408	29,800
Women <50 years old (%)	62	40	36	52
Breast cancer incidence per 1000				
Tamoxifen	4.7	3.4	2.1	4.7
Placebo	6.7	5.5	2.3	6.7
Side effects				
Endometrial cancer[a]	13/5	36/15	_	13/5
Tamoxifen/placebo	14/9	35/22	_	64/38
Pulmonary embolism	Not reported	18/6	_	44/32

[a]Endometrial cancer was only significantly evaluated in postmenopausal women

be treated to benefit two or three individuals annually. (2) The side effects of tamoxifen are great enough to convince high-risk women not to engage in this strategy.

Despite the fact that tamoxifen is the first FDA-approved preventive, the strategy is both unrealistic and imprecise. Indeed, physicians themselves discount chemoprevention, and recent studies show there is a remarkable lack to knowledge by general practitioners concerning the potential benefits for select high-risk women [119]. The solution for society was the discovery of SERMs, which will be considered in the companion chapter.

9 Conclusion

Tamoxifen is a successful lifesaving drug because of the translational research strategy of targeting the breast tumor ER and applying long-term adjuvant therapy. There were initial faltering steps toward development of the clinical strategy. Most importantly, an anti-estrogenic medicine was an unlikely path to progress competing in a world dominated by cytotoxic chemotherapy that was predicted to cure cancer. Nevertheless, individuals working together in concerts made the medicine become a pioneer, as the first of a new group of medicines called SERMs.

Personal Postscript V. Craig Jordan

Dr. Elwood Jensen dedicated his career to describe the target for successful therapeutics in breast tumor—the ER. His basic work in the early 1960s established the presence of ER in estrogen target tissues, e.g., uterus, vagina, and pituitary gland of laboratory rats [15, 16]. His collaborative team of clinicians then translated the laboratory research to patients [120] with metastatic breast cancer. The team found a positive correlation between ER in MBA and adrenalectomy. Breast cancer that was ER-negative was less likely to respond. This work catalyzed efforts to create the ER assay in breast tumors in order to predict whether patients would respond to ablative endocrine therapy, i.e., oophorectomy, adrenalectomy, or hypophysectomy [121].

The nonsteroidal anti-estrogen ICI46,474 was discovered in the 1960s in the fertility control program at Alderley Park, the research headquarters of ICI Pharmaceuticals Division in Cheshire, England [26]. The description in the patent was: “The alkene derivatives of the invention are useful for the modification of the endocrine status in man and animals and they may be useful for the control of hormone dependent tumors or for the management of the sexual cycle and aberrations thereof. They also have useful hypocholesterolaemic activity.” The patent history of tamoxifen is unique. The United Kingdom patent was published in 1965 but denied in the United States until 1985. Merrell had defensive patenting of triphenylethylenes. By the time patent protection was lost everywhere in the world but America, where there was no patent, the 17-year patent life started. This was just as the NCI recommended adjuvant tamoxifen therapy as standard of care [122].

In the 1960s, the team of Dr. Dora Richardson (chemist) had synthesized the substituted triphenylethylene (Fig. 10) and separated the product into pure *cis*- and

Fig. 10 The principal players in the discovery of ICI 46,474 at ICI Pharmaceuticals Division, Cheshire, UK, in the 1960s that eventually evolved into tamoxifen a decade later. Arthur Walpole (Walop) (left) was the head of the fertility control program tasked with the mission to discover safer compounds to "regulate the sexual cycle." Dora Richardson (center), the team organic chemist who synthesized all of the isomers of the triphenylethylene derivatives that would be tested as antifertility agents in rats by Mike Harper, the team reproductive endocrinologist. Arthur Walpole would be VCJ's PhD examiner, scientific supporter, and administrative link to ICI until his untimely death on July 2, 1977. Dora Richardson would provide the metabolites of tamoxifen to the author to be tested as anticancer agents, and Mike Harper would offer the author a 2-year BTA (Been to America) at the Worcester Foundation, MA. Each individual was generous with important opportunities, investment, and support for a young investigator starting their adventure to investigate "failed morning after pills" as future important therapeutic agents in women's health

trans-isomers [28]; Dr. MJK Harper (reproductive biologist) and Walpole had described the *cis*-isomer, ICI 47,699, as an estrogen in rats and mice and the *trans*-isomer ICI 46,474 as an anti-estrogen in rats but with weak estrogen-like actions [10]. Strangely enough ICI 46,474 was classified as an estrogen both in mouse vaginal cornification assays [10] and in immature mouse uterine weight tests [123]. This biological knowledge was pivotal for the subsequent discovery of SERMs some 20 years later at the University of Wisconsin, Madison.

However, by 1972, all clinical data was reviewed at ICI Pharmaceuticals Division and the decision made to terminate development [124]. The product was not predicted to recover sufficient revenues to support marketing in the niche area of the induction of ovulation in subfertile women and the treatment of metastatic breast cancer. In the case of MBC, only one in three tumors responded, and responses were only for a year or 2. The head of the fertility control program at ICI Pharmaceuticals Division in 1972 was Dr. Arthur Walpole [125]. He chose to take early retirement if ICI 46,474 was abandoned for clinical development as a drug to treat breast cancer.

In 1972, I was completing my PhD at Leeds University, Department of Pharmacology, on the structure function relationships and contraceptive properties of nonsteroidal anti-estrogens in mice. However, no academic faculty member in the United Kingdom would agree to examine my thesis on "A study of the oestrogenic and anti-oestrogenic activities of some substituted triphenylethylene and ethane's" (or failed contraceptive for short!), but this is how life takes an unpredictable turn.

The research facility for ICI Pharmaceuticals in Cheshire, Alderley Park [26], was 10 miles from my home. In 1967, I had wanted to be a summer student at Alderley Park, but how could I get an interview. I had read Dr. Steven Carter's publications in Nature [126]. He was a cell biologist at Alderley Park studying mouse cancer cells. Cancer research is what I wanted to do. I decided to take a bus to Alderley Park and phoned Dr. Carter from the phone box outside the research facility. I was connected to Dr. Carter through the Alderley Park Operator—"Hello Dr. Carter, my name is Craig Jordan and I am a student at the University of Leeds, but I live nearby Alderley Park in Bramhall. I have read your publications in Nature on cytochalasins and I wonder whether you had room in your laboratory for me as a summer student?" He replied "Next time you are home in Bramhall, arrange to have an interview with me." I told him I was calling from outside the front gate of Alderley Park. He invited me in immediately and I got the job!

I was excited, as a pharmacology student at the University of Leeds, to be witnessing research and discovery first hand. I learned electron microscopy, listened to all of their weekly research lectures, and spent hours in their library. I was in heaven! By strange coincidence, years later, cytochalasins were used in rat pituitary tumors GH_3 cells to demonstrate that the unoccupied ER was located in the nucleus [127]. The same technique was used in my laboratory using MCF-7 breast cancer cells [128].

In the cardiovascular laboratory next door to Dr. Carter's laboratory was Dr. Michael Barrett. He was head of the β-blocker program at Alderley Park. Dr. Walpole's fertility control group had laboratories opposite to Dr. Carters'. Dr. Walpole had just published his papers on ICI46,474 [10, 31]. I went out for lunch in Alderley Edge each Friday with all of his laboratory staff. All the scientists who would later influence my life surrounded me that summer in 1967.

In 1971, Professor Michael Barrett became head of the Department of Pharmacology at the University of Leeds. He recruited me to be a lecturer in pharmacology and convinced the university authorities that Dr. Walpole would be an appropriate examiner for my PhD thesis despite the fact that he was "from industry." Professor Barrett and Dr. Walpole secured a 2-year visiting scientist position for me working at the Worcester Foundation for Experimental Biology (WFEB) in America. Their friend and former colleague Dr. Michael Harper was working to produce a once-a-month contraceptive based on the emerging pharmacology of prostaglandins. Therefore, off to the WFEB, I went to immerse myself in contraception research.

The WFEB is the "home of the oral contraceptive," but what I really wanted to do, as a pharmacologist, was to devise medicines to treat cancer. However, this was considered a very high-risk enterprise. Few were interested, in new therapeutic methods of treating cancer, as the favored approach was to use combination cytotoxic chemotherapy. Numerous toxic side effects for patients were life threatening. Nevertheless, cytotoxic chemotherapy was predicted to cure all cancers despite the fact that the therapy also targeted normal dividing cells.

When I arrived at the WFEB, I was shocked to discover that my supervisor, Dr. Michael Harper, had planned to leave immediately as he had secured a position at

the World Health Organization heading their contraception program. My new boss Dr. Edward Klaiber (Fig. 11) was most generous, allowing my family to stay at his home in Princeton, MA, while he and his wife Jennie were in Austria for 2 weeks. He even lent me his car, an unheard event in England! Dr. Klaiber said that I should plan my 2 years of work on prostaglandins. He had inherited the large contraception program grant awarded by the USAID to Dr. Harper, and that grant was paying my salary. Other than that, I was free to study anything I liked as long as I got funding. That was the WFEB way. By lucky chance, in 1971, President Nixon had signed the National Cancer Act. The goal was to take treatment strategies and new medicines from the bench to the bedside. Now was my opportunity to work on cancer.

I was unaware that ICI46,474 was not planning to develop ICI46,474 despite having low toxicity and showing modest activity in MBC [27]. The advantage of tamoxifen compared with other endocrine therapies was reduced side effects. Clomiphene had been successfully tested earlier [129] so the approach was not new. A phone call to Dr. Walpole secured his support to study ICI46,474 in the laboratory, but he had to arrange with Stuart Pharmaceuticals, ICI's new acquisition in Wilmington, Delaware, to provide funding. He succeeded and I met the drug monitor for ICI46,474 Lois Trench (Fig. 12). She was tasked with initiating clinical studies, and she claimed I was just what she needed, a scientist who knew the literature on anti-estrogens. I had knowledge of current thinking about the ER and would

Fig. 11 The award of an honorary Doctor of Science degree from the University of Massachusetts (2001) for laboratory work started at the WFEB that resulted in the evaluations of tamoxifen for the prevention of breast cancer in high-risk women. On the right of Dr. Jordan is Dr. Edward Klaiber and his wife Jeannie (far right). Dr. Klaiber was Dr. Jordan's "boss" at the WFEB

Fig. 12 Lois Trench and Dr. Elwood Jensen on the occasion of Dr. Jordan's investiture as the Diana, Princess of Wales, Professor of Cancer Research at Northwestern University (1999). Lois Trench the energetic and committed clinical monitor for ICI America for tamoxifen clinical trials in North America. She accomplished the FDA approval of tamoxifen in America in record time on December 30, 1977. Lois is the godmother of Dr. Jordan's daughter Alexandra

subsequently speak to clinicians from the Eastern Cooperative Oncology Group (ECOG) and the National Surgical Breast and Bowel Project (NSABP). However, the problem I was tasked with by Dr. Walpole was (to paraphrase) "we will put tamoxifen on the market, your task is to devise a strategy how best to use the medicine." Even to me it was obvious that treating MBC with tamoxifen was futile; everybody died. I planned first to train myself in methods in cancer research pertaining to breast cancer but how? That problem was solved for me by the signing of the National Cancer Act in 1971 and now being free to do research at the WFEB.

Dr. Elwood V. Jensen (Figs. 12 and 13), Director of the Ben May Laboratory for Cancer Research at the University of Chicago, had been appointed, to the Scientific Advisory Board of the WFEB. He was asked to encourage the exploitation of the rich knowledge of endocrinology at the foundation but now to apply it to cancer research and treatment. Dr. Jensen was to visit the WFEB in late 1972. I, as the only person with in-depth knowledge of estrogen and anti-estrogen action, was asked to make myself available to meet Dr. Jensen.

I was invited to go out to dinner in Worcester with a small group of faculty to entertain Dr. Jensen. During the following day, Dr. Jensen and I were to meet for scientific discussions. I explained my ideas for ICI46,474 and showed him my thesis on "failed contraceptives." Later in the afternoon, he gave a major presentation before the whole of the WFEB. Imagine my surprise when he mentioned our discussion about ICI46,474 and my plans for new strategies to treat breast cancer.

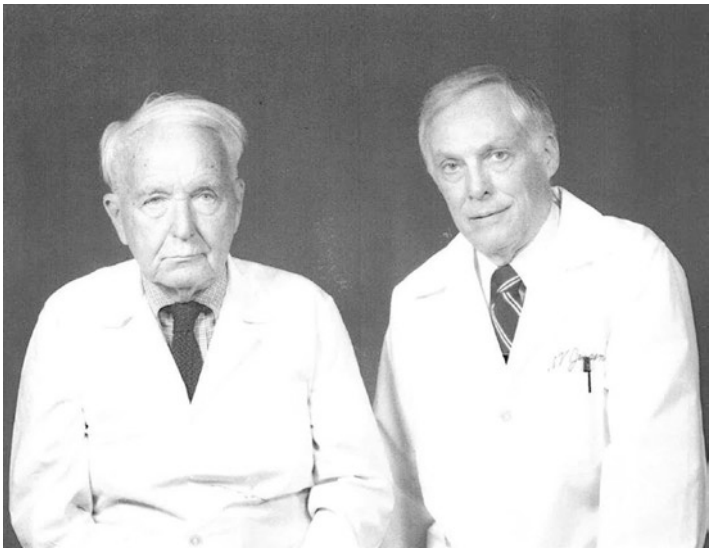


Fig. 13 Professor Charles Huggins (left) and Elwood Jensen, the founding Director and subsequent Director of the Ben May Laboratory for Cancer Research at the University of Chicago. Huggins was to receive the Nobel Prize in Physiology and Medicine for his work on androgen action and Jensen the Lasker Award for estrogen action

Following our meeting in late 1972, Dr. Jensen (Fig. 12) invited me to Chicago to learn ER assays on breast tumors. I was taught by Sylvia Smith and Elwood's staff at the Ben May Laboratory for Cancer Research. Additionally, I met the Nobel Laureate and former Director, Professor Charles Huggins (Fig. 13). At the Ben May Laboratory, Dr. Gene DeSombre taught me the DMBA-induced rat mammary carcinoma model (aka the "Huggins model") [130].

The WFEB had secured a contract from the NCI to measure ER in breast cancer. To expand our knowledge, Drs. Chris Longcorpe, David Kupfer, and I went off to San Antonio to learn ER measurement techniques in Dr. Bill McGuire's laboratory. Some of our analytical results on endometrial cancers were subsequently published [131]. Armed with all this cutting-edge technology and the DMBA model, I set about my task to initiate a systematic study of the anticancer actions of tamoxifen (still ICI46,474 at the time). My first experiment, and my first paper, replicated a study of high-dose subcutaneous injections of H774 and H1076, in ovariectomized mice [132, 133] published by Professor Cliff Emmens in Australia. These nonsteroidal anti-estrogens were similar to tamoxifen, so I used tamoxifen instead. Initial estrogenic effect on ovariectomized mouse vagina occurred for about a week, but then the vagina became refractory to estrogen stimulation for 6 weeks thereafter [134]. This, my first publication (single author as I did all the work), was accepted with two minor spelling changes. Well that never happened again! I was, however, formulating an idea that perhaps depot injections of tamoxifen might be the way to

prevent breast cancer in women. First, I chose to address a controversy that some investigators could not demonstrate that tamoxifen blocked estrogen binding to the ER. This was addressed using sucrose density gradient analysis at the WFEB using the technique and equipment provided by Dr. Jensen. The result was clear. In both breast and endometrial tumors, tamoxifen blocked the binding of [^{3}H] estradiol to the 8S estrogen receptor [135]. So if the ER was a drug target, could a couple of tamoxifen injections prevent DMBA-induced rat mammary carcinogenesis? Again, the results were clear; two consecutive peanut oil sc injections of 5 mg tamoxifen given simultaneously with 20 mg of DMBA to 50-day-old female Sprague-Dawley rats inhibited rat mammary carcinogenesis by 95%! News traveled fast at the foundation, and Dr. Ferdinand Peron came into my lab exclaiming "My God, you have cured cancer; tell me about it!" I explained it was obvious. If oophorectomy prevents rat mammary carcinogenesis, then an "anti-estrogen" should accomplish the same result. I wrote up my work for the European Journal of Cancer and sent it off. The three referees recommended rejection, but one referee (I suspect Dr. Walpole) made a list of good suggestions, which I followed when I returned to Leeds. I did additional well-controlled experiments, and my paper was rewritten, resubmitted, and accepted [113].

I also submitted an abstract to the International Congress of Steroid Endocrinology in Mexico City. This abstract was accepted and presented orally. Dr. Marc Lippman then at the National Cancer Institute, heading their Breast Cancer Program, asked several questions because he too was seduced into tamoxifen research by Lois Trench. He subsequently published an important paper in Nature [58] in 1975. Indeed, it was that paper and the statement "the phenomenon of tamoxifen killing is invariably reversible if estradiol is added to the medium by 48 hours even though the anti-estrogen remains in the medium." That observation led me to address the issue of adjuvant therapy with tamoxifen. How long was long enough to control recurrence if tamoxifen was used as an adjuvant therapy? Did tamoxifen destroy breast cancer cells in vivo? At that time, the clinical community had selected 1 year of tamoxifen after mastectomy because they knew that tamoxifen only controls MBC for a year or 2 [103]. Maybe this strategy would work if tamoxifen did kill breast cancer cells.

Back at the Department of Pharmacology, at the University of Leeds, we chose to complete a study of dose escalation for 1 month of treatment starting at 1 month after the oral administration of 20 mg DMBA dissolved in peanut oil. The scientific goal was to determine whether tamoxifen could kill the micro-foci of precancerous and early microscopic mammary cancer.

Karen Allen (now Porter) and my PhD student Clive Dix showed that increasing daily sc doses of tamoxifen administered for a month caused a dose-dependent delay in mammary carcinogenesis [136–138]. Knowledge that the injections of the lipophilic compound ICI46,474 formed a depot for slow release, and the fact that tamoxifen has a long half-life in animals and humans [42, 43], led to the conclusion that continuous treatment was necessary to suppress rat mammary carcinogenesis completely [137, 138]. So it proved to be.

These data were obtained because of the financial investment of Dr. Arthur Walpole, Roy Cotton (the initial physician at ICI Pharmaceuticals Division responsible for initiating the clinical development of tamoxifen), and Brian Newbold (Research Director) into the laboratory of a young scientist with a plan "to target the ER in breast cancer, to use long-term adjuvant tamoxifen therapy (my battle cry was 'tamoxifen forever'), and open the door for chemoprevention studies with tamoxifen." On July 2, 1977, Arthur Walpole died suddenly. This was only 6 months after his recruitment. I attended the church service with the ICI pharmaceuticals staff, and at the time, the Research Director, Dr. Brian Newbold, reassured me that Alderley Park would maintain its support for my progress at the University of Leeds. We were now making enormous progress with my new strategy, but Dr. Walpole, my friend and supporter, would never see the results of his discovery of ICI46,474.

In 1978, the Pharmaceuticals Division was to receive the Queen's Award for Technological Achievement (Fig. 14a–c). At the luncheon, I discovered I was the only nonmember of Alderley Park to be invited. I sat with Drs. Sandy Todd and Roy Cotton, both who were so supportive at the beginning and remain lifelong friends. However, laboratory data and scientific publications are all fine. The good news was that the strategies proposed were proposed on solid data. These data were facts not opinions. The path to progress in medical oncology, however, is by convincing the medical establishment to change!

In September 1977, I was invited to present a talk at a clinical meeting for physicians at King College, Cambridge. The meeting was sponsored annually by ICI Pharmaceuticals Division to educate physicians (Fig. 15a–c). I presented my new adjuvant therapy strategy. Resistance was vigorous with objections that the animal model did not replicate human breast cancer. Indeed, it was dangerous because to paraphrase "we know that tamoxifen is effective only for a year or 2 in the treatment of metastatic breast cancer, so your approach will encourage early resistance to tamoxifen. We will have wasted a valuable palliative medicine to use at the end of life. In fact your approach is dangerous for patients!"

Later that month, in 1977, I traveled to the University of Wisconsin Clinical Cancer Center in Madison, as Lois Trench was trying to get them to recruit me to come to America. I presented the expanded talk and included the new chemoprevention data. Dr. Harold Rusch, then Director of the UWCCC, and Dr. Paul Carbone, Chairman of the Department of Human Oncology, decided to offer me a job on the spot [139]. I had a plan, and they had an embryonic Clinical Cancer Center funded 6 years earlier as a result of the National Cancer Act. By contrast, in Britain there was continuing medical resistance to the use of the ER assay to select patients for tamoxifen treatment. This was based on poor ER/patient response data in the NATO trial and the Scottish trial [140, 141]. Indeed much laboratory work was focused on the biological rational of why tamoxifen was an anticancer agent in ER-negative breast cancer [142]. Indeed, during the 1980s, I was informed that at some hospitals all patients were given tamoxifen.

Through a multitude of clinical trials worldwide, but most importantly the Early Breast Cancer Trials Collaborative Group (EBCTCG) in Oxford, solid conclusions were made about the veracity of the translational research: the ER is the essential

July 14, 1978

Scan

ICI Pharmaceuticals Division's Newspaper

1975 1978

AN OCCASION FOR PRIDE

THE COLLECTIVE EFFORTS of everybody in Pharmaceuticals Division — from senior management to the most junior employee — were praised by the Lord Lieutenant of Cheshire, Viscount Leverhulme, last week when he presented the Queen's Award for Technological Achievement.

The Queen's representative in Cheshire told 230 employees and guests in the Mereside restaurant: "Every single person in your Division can be proud of this fine achievement".

Viscount Leverhulme spoke of his "very real pleasure" in visiting Alderley Park to present the Division with its ninth Queen's Award and the seventh which he personally had handed over.

He said the latest award recognised the outstanding technological achievement behind 'Nolvadex', the Division's anti-oestrogen drug used in the treatment of advanced breast cancer.

Exports

He added that the science and technology which led to 'Nolvadex' had also resulted in substantial export achievement, with overseas sales now accounting for nearly 70 per cent of the product's total sales. It was making a significant contribution to the exports on which the wellbeing and prosperity of the nation depended.

Viscount Leverhulme recalled that when he first visited Alderley Park in 1966, he had the pleasure of presenting the first Queen's Award gained by an industrial concern in Cheshire.

The awards were conferred very sparingly, he said, and this year the Division had gained one of only two in Cheshire — and both had gone to ICI. Mond Division had also won an award for technology.

"Cheshire today shares your pleasure and your pride in winning this splendid award," said Viscount Leverhulme. "My very warm and very sincere congratulations to all of you."

Division Chairman Peter Cunliffe, after receiving the award from Viscount Leverhulme, commented that technological achievement and exports went hand-in-hand in Pharmaceuticals Division.

"We have always believed that the pharmaceutical industry is particularly suited to the UK", said Mr. Cunliffe.

"We are, as a nation, good at research. We invent products which meet the needs of people throughout the world and we therefore contribute significantly to the UK balance of payments.

"The UK itself represents only a small proportion of the world prescription market — something like three per cent of the total — so the invention of each new pharmaceutical product creates the opportunity for exports from this country."

Mr. Cunliffe said the success of a product like 'Nolvadex' was the result of the efforts of all employees both in the UK and overseas.

Research

First and foremost came the research effort which made everything else possible. Then the product had to be developed and manufactured and finally it had to be marketed by staff at home and overseas.

"It is particularly pleasing that this award should be for a product for the palliative treatment of breast cancer," he continued.

"It is a public recognition of the work of the Division's employees and also of the value of that work to the health and wellbeing of this country and indeed the world.

"As I have said on a previous occasion, we are doing a worthwhile job and doing it well."

Most of the staff who were directly involved in the research and development project were present, among more than 200 staff selected by ballot or other means to represent their departments, sites or associated companies.

The Lord Lieutenant of Cheshire, Viscount Leverhulme, presents the Queen's Award to Division Chairman Peter Cunliffe. In the centre is the Mayor of Macclesfield, Councillor D. B. Kingston.

Dora Richardson, the chemist who synthesised the first sample of 'Nolvadex', had a place of honour on the top table. Also pictured (left to right), are biologist Barry Furr, another central figure in the research project, Deputy Chairman Alan Hayes, Viscount Leverhulme, the Division Chairman and the Mayor of Macclesfield.

Harry Gallagher, now retired, who made a vital contribution to process development, is seen (centre) at the bottom of this table, on which there were representatives from Process Development, Pharmacology, Industrial Property and Medical Aids Departments.

Staff from the Clinical Research and Development Departments who have been closely involved with the 'Nolvadex' project. Representatives of Operations Department were also on this table. On the right (front) is Craig Jordan, from Leeds University, who contributed to the pharmacological work.

Biology and Biochemistry Departments, where many of the early problems were solved, were represented by these staff.

'A fine achievement'

Fig. 14 The Queen's Award for Industry is the highest recognition possible. It recognizes outstanding achievement by industry to aid the country's economy. The award made by the Lord Lieutenant of Cheshire, Viscount Leverhulme, the Queen's representative, in July 1978, was celebrated by 230 handpicked employees, who were recognized for their role in the drug development of tamoxifen. Dr. Walpole, the team leader and champion of tamoxifen development, had died the year earlier and never saw the success of his invention. Dr. Roy Cotton (sitting opposite from Dr. Jordan in panel **c**) was the initial clinical monitor for tamoxifen development. He was advised not to spend too much time on tamoxifen as it was not predicted to be a successful product. However, Fig. 14 (continued) Dr. Jordan's strategy that came out of their investment at the WFEB and Leeds University for 7 years proved successful. Dr. Jordan (his personal invite as 14b) was the only one for a person not working for Pharmaceuticals Division


THE CHAIRMAN AND DIRECTORS OF
THE PHARMACEUTICALS DIVISION
of
IMPERIAL CHEMICAL INDUSTRIES LIMITED
request the pleasure of the company of
DR. CRAIG JORDAN
at a luncheon in the Mereside Restaurant, Alderley Park
at 12 noon for 12.30 p.m. on Thursday 6th July 1978
on the occasion of the Presentation to the Division
of
THE QUEEN'S AWARD TO INDUSTRY
by
H.M. Lord Lieutenant for the County of Chester
The Rt. Hon. THE VISCOUNT LEVERHULME, T.D.
R.S.V.P. E. G. Thompson, Personnel Department, Alderley House

(b)

(c)

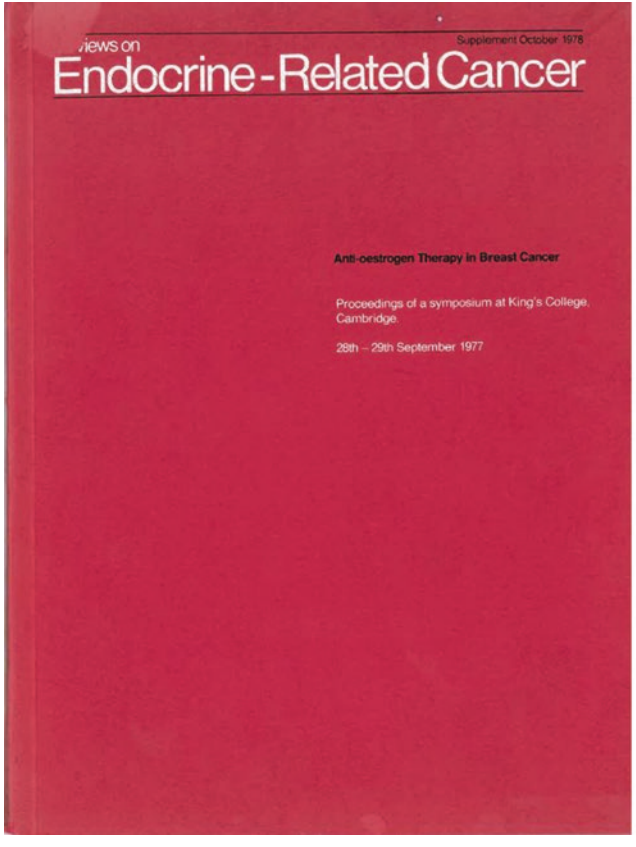
Fig. 14 (continued)

marker for tamoxifen activity; lives are saved [143]. Those lives saved depend upon the duration of tamoxifen administration; longer is better [110].

After an interlude in Switzerland (1979–1980) designing and building a new Ludwig Institute for Cancer Research in Bern, I was to find myself in the right place at the right time and closer to Dr. Elwood Jensen, the Director of Ben May Cancer Laboratories in Chicago. However, he was about to travel to Zurich, Switzerland, where he would be the Director of all the Ludwig Institutes for Cancer Research worldwide. Never could I have imagined that 20 years later, Elwood and I would be the co-recipients of the then highest award from the AACR. This is the inaugural Dorothy P. Landon award for translational cancer research in 2002 (Fig. 16a–c). He defined the tumor target, and I provided the lifesaving strategy to use tamoxifen as a long-term adjuvant treatment for patients with ER-positive primary breast cancer.

Over the decades, Elwood would write numerous letters of support for me to receive awards or promotions. At the start of my journey with tamoxifen, never would I have believed we would both be members of the national Academy of Sciences. Indeed, it would never have occurred to me that the University of Leeds and AstraZeneca would co-nominate me for consideration for an Order of the British Empire (OBE) for my role in the "tamoxifen tale." It was the late Barry Furr (Fig. 17a, b), the Chief Scientist at AstraZeneca, who wrote my citation based on not only my laboratory studies funded by ICI Pharmaceuticals Division in the 1970s but also my role as an expert witness for AstraZeneca to defend their patents in the United States during repeated challenges in the 1990s. The Smalkin decision in Baltimore in 1996 was a true education. I found this a unique experience. It turned out that not only did Judge Smalkin have an interest in British military history but also discovered that I was a Regular Army Reserve Officer in the British Special Air Service (SAS). This is the premier Special Forces regiment in the world. He spoke to me directly from the bench during my testimony, about matters pertaining to the SAS members, much to the confusion of the lawyers! Subsequently, I discovered

Fig. 15 (**a**) Participants at a Breast Cancer Symposium in September 1977 at Kings College, Cambridge, England. The concept of extended adjuvant tamoxifen treatment was first proposed at this meeting. Clinical studies of a 1-year adjuvant tamoxifen were in place; regrettably, a decade later this approach was shown to produce little survival benefit for patients. In the insets (top), the author, who presented the new concept (bottom left); Professor Michael Baum, the session chairman who was about to launch the Nolvadex Adjuvant Trial Organization (NATO) 2-year adjuvant tamoxifen trial; and (bottom right) Dr. Helen Stewart, who was a participant at the conference. She would initiate a pilot trial in 1978 and, led by Sir Patrick Forest, would later guide the full randomized Scottish trial of 5 years' adjuvant tamoxifen treatment vs. control in the 1980s. Both clinical trials were later proven to produce survival advantages for patients. The concept of longer tamoxifen treatment producing more survival benefits for patients was eventually established indirectly by the Oxford Overview Analysis in 1992 and directly by the Swedish group led by Dr. Lars Rutqvist. (**b**) The front of the program for the symposium. (**c**) The closing statement that by targeting the ER-positive breast cancers with long-term adjuvant tamoxifen therapy would be an appropriate clinical trials strategy

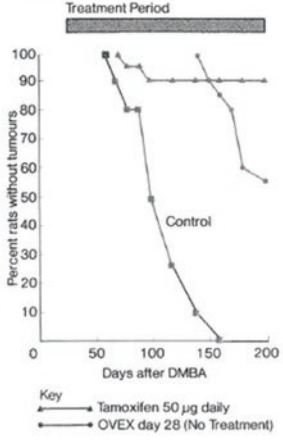


as the drug is cleared from the body. Therefore in this case Tamoxifen would appear to have a suppressive effect rather than a tumour specific killing effect.

Continuous treatment

The effect of ovariectomy on day 28 after DMBA followed by no further treatment was compared to a continuous Tamoxifen therapy (50 mcg/day) from day 28. By 150 days all 20 rats in the control group had tumours. In the ovariectomized group tumours started to appear by 150 days after DMBA and at 200 days after DMBA only 45% of the rats in the group were tumour free. Thus ovariectomy appears to retard tumour development rather than completely protect the animals from the carcinogenic process. The Tamoxifen-treated group by comparison produced a few tumours by 100 days after DMBA but then no more and by 200 days 90% of the rats were tumour free.

Figure 7
Reduction in the number of rats with a tumour after continuous treatment with Tamoxifen.



Conclusions

These studies show that, as in the human situation, once the tumours have become established it is difficult to effect a complete cure with Tamoxifen treatment.

The oestrogen receptor appears to play a role in the control of tumour growth in this particular model, although we cannot precisely predict how the tumour will respond to treatment. It does seem though, that if oestrogen receptors are low or absent then the tumour is probably hormone independent and the anti-oestrogen will be ineffective. By contrast to the treatment of animals with a large tumour burden, a short course of Tamoxifen treatment during the early development of tumours will produce some protection of the animal by suppressing the small foci of deranged cells. Perhaps most effective though is a continuous course of Tamoxifen therapy which appears to be very effective in suppressing tumour development.

Our data in the DMBA-induced rat mammary carcinoma model suggests that an adjuvant type of treatment is effective in controlling tumour growth and development and would warrant the establishment of controlled clinical trials.

Acknowledgements

I would like to thank Mr Clive Dix for his invaluable assistance during these studies.

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Fig. 15 (continued)

American Association for Cancer Research

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Chief Executive Officer

February 20, 2002

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Dr. V. Craig Jordan
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Dear Drs. Jensen and Jordan:

I have the great pleasure to officially notify you that the American Association for Cancer Research has chosen to recognize your exemplary contributions to cancer research by naming you the co-recipients of the First Dorothy P. Landon-AACR Prize for Translational Cancer Research.

This Prize is one of two awards newly established by the Kirk A. and Dorothy P. Landon Foundation and the AACR. The Prize that you will receive seeks to promote and reward seminal contributions to our understanding of cancer through outstanding translational cancer research at the cutting edge of scientific novelty and significance.

The Selection Committee received a large number of nominations of excellent candidates, and you were chosen as the most worthy scientists from among an impressive pool of candidates.

The Selection Committee chose to honor both of you for your individual research contributions, which, when considered together, represent the realization of a tremendous advance in translational cancer research. This Prize recognizes that your research resulted in the first molecular targeting that has saved hundreds of thousands of lives and opened the door to practical chemoprevention.

Dr. Jensen, you were cited as a true pioneer in the field of endocrinology and cancer. Your identification of the estrogen receptor, and subsequent studies refuting the prevailing view of estrogen action, has clearly shifted our understanding of the action of steroid hormones and has advanced cancer treatment. The Committee also noted your achievements in purifying the receptor, making the first polyclonal and monoclonal antibodies, and contributing to the cloning of the estrogen reception cDNA. The result of these discoveries led to later studies linking ER to prognosis and treatment response in breast cancer.

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Dr. Jordan, you were cited by the Committee for your pioneering laboratory work in defining estrogen action at the cellular and molecular level, your seminal work on the function of ER antagonists, and your recognition of the potential of tamoxifen for the treatment and prevention of breast cancer. Your studies elucidated that inhibition of estrogen action plays a fundamental role in the anti-tumor effects of tamoxifen. Your further studies of the metabolic activation of nonsteroidal antiestrogens, the differences between estrogen and antiestrogen-estrogen receptor complexes, the species-specific pharmacology of antiestrogens, and other finding formed the basis for the potential clinical applications of selective estrogen receptor modulators (SERMs).

The Committee agreed that the symbiosis between your respective bodies of work has resulted in a dramatic strategic change in the approach to the treatment of cancer, and is one of the most successful examples of translational cancer research.

As the recipients of this Prize, you are asked to co-deliver an hour-long lecture during the 93rd AACR Annual Meeting, to be held in San Francisco, California, on Sunday morning, April 7, 2002, in Hall D of the Moscone Convention Center. The lecture will follow the presentation of the Award by the Chairperson of the Selection Committee, Dr. Joseph R. Bertino, and the Chairman of the Landon Foundation Board, Mr. R. Kirk Landon.

You will each receive a commemorative gift from the Foundation;; complimentary registration; support for your travel, housing, and subsistence expenses to attend the Annual Meeting; and equally share an unrestricted cash prize of $200,000.

Feel free to contact Ms. Victoria A.M. Wolodzko, Manager, Program Administration at (215) 440-9300, ext. 136 or via e-mail to wolodzko@aacr.org, if you have any questions at this time. Ms. Wolodzko and her staff will follow up with additional logistical information about your lecture and your travel to San Francisco.

Please accept my heartfelt congratulations on this signal achievement in your career.

With best regards,

Margaret Foti, Ph.D.
Chief Executive Officer

MF/vamw

Fig. 16 (**a**) The presentation of the inaugural Dorothy P. Landon/AACR Award for Translational Research by AACR President Ki Hong, MD, and the Chairman of the Landon Prize evaluation committee Dr. Joseph Bertino in 2002 to Dr. Elwood V. Jensen and Dr. V. Craig Jordan. (**b**) The letter of the inaugural Dorothy P. Landon/AACR Award for Translational Research award with citations for Dr. Elwood V. Jensen and Dr. V. Craig Jordan

Fig. 17 (**a**) Dr. Barry Furr, Chief Scientist at AstraZeneca, at the investiture of Dr. Jordan as the Diana, Princess of Wales, Professor of Cancer Research. Both Dr. Furr (left) and Dr. Jordan (right) were presenters in the symposium in Dr. Jordan's honor. (**b**) The day following Dr. Jordan's investiture as Officer of the Most Excellent Order of the British Empire by her Majesty Queen Elizabeth II, senior staff held a celebration dinner in Alderley Edge near ICI Pharmaceuticals Division Alderley Park. There Dr. Jordan was presented with an antique map of Cheshire by the pioneering historian and mapmaker, John Speed. Speed was a Cheshire man. Craig Jordan's maternal family (Mottram) and Alderley Park are all in Cheshire within 10 miles of each other. The framed map is from Speed's original collection from 1611. The map is from his book, *The Theatre of the Empire of Great Britain*, which was signed on the back by all the guests from the original Alderley Park team in the 1970s

that Judge Smalkin mentioned me by name in his ruling for the veracity of my cross-examination of the stand. I am told this usually doesn't happen for expert witnesses. AstraZeneca earned many billions of dollars, as a result of exclusive tamoxifen sales, in the United States.

I thank the late Arthur Walpole (PhD examiner and academic supporter), the late Barry Furr (early friend in the 1970s and subsequently Chief Scientist), Dr. Roy Cotton, Lois Trench, and Dr. Brian Newbold for taking a chance on a young scientist with a plan to realize the full potential of tamoxifen.

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