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The Evolution of Nonsteroidal Antiestrogens to become Selective Estrogen Receptor Modulators

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Abstract

The discovery of the first nonsteroidal antiestrogen ethamoxytriphetol (MER25) in 1958, opened the door to a wide range of clinical applications. However, the finding that ethamoxytriphetol was a “morning after” pill in laboratory animals, energized the pharmaceutical industry to discover more potent derivatives. In the wake of the enormous impact of the introduction of the oral contraceptive worldwide, contraceptive research was a central focus in the early 1960’s. Numerous compounds were discovered eg: clomiphene, nafoxidine, and tamoxifen, but the fact that clinical studies showed no contraceptive actions, but, in fact, induced ovulation, dampened enthusiasm for clinical development. Only clomiphene moved forward to pioneer an application to induce ovulation in subfertile women. The fact that all the compounds were antiestrogenic made an application in patients to treat estrogen responsive breast cancer, an obvious choice. However, toxicities and poor projected commercial returns severely retarded clinical development for two decades. In the 1970’s a paradigm shift in the laboratory to advocate long term adjuvant tamoxifen treatment for early (non-metastatic) breast cancer changed medical care and dramatically increased survivorship. Tamoxifen pioneered that paradigm shift but it became the medicine of choice in a second paradigm shift for preventing breast cancer during the 1980’s and 1990’s. This was not surprising as it was the only medicine available and there was laboratory and clinical evidence for the eventual success of this application. Tamoxifen is the first medicine to be approved by the Food & Drug Administration (FDA) to reduce the risk of breast cancer in women at high risk. But it was the re-evaluation of the toxicology of tamoxifen in the 1980’s and the finding that there was both carcinogenic potential and a significant, but small, risk of endometrial cancer in postmenopausal women that led to a third paradigm shift to identify applications for selective estrogen receptor (ER) modulation. This idea was to establish a new group of medicines now called Selective ER Modulators (SERMs). Today there are 5 SERMs FDA approved (one other in Europe) for applications ranging from the reduction of breast cancer risk and osteoporosis to the reduction of menopausal hot flashes and improvements in dyspareunia and vaginal

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lubrication. This article charts the origins of the current path for progress in women's health with SERMs.

Keywords

breast cancer; osteoporosis; women's health; endometrial cancer

Introduction

Today tamoxifen (Fig. 1) is part of the fabric of our society: almost everyone knows someone who is alive today because of their treatment with this antiestrogen used to prevent breast cancer recurrence. But this medicine is not only a pioneering breast cancer treatment and chemopreventive, but also a drug so thoroughly researched in the laboratory (I (VCJ) would always say this was to reveal "the Good, the Bad, and the Ugly") that a whole new group of medicines, the Selective Estrogen Receptor Modulators (SERMs) was created to address specific tasks in therapeutics. This saga, that first started in 1958 (1) with the report of the first nonsteroidal antiestrogen MER25 (Fig. 1) will twist and turn as fashions and priorities in medical research changed. Many nonsteroidal antiestrogens were synthesized initially when it was thought that there was great potential for their use as "morning after pills" but this application was not to occur as the compounds guaranteed what they were designed to prevent in women! The long gestation period for nonsteroidal antiestrogens resulted in clomiphene (Fig. 1), the first medicine to induce ovulation in women (2) in the 1960's, and then the orphan drug tamoxifen would be approved almost by chance, for the treatment of metastatic breast cancer in the 1970's. Tamoxifen stood the test of time as a pioneering breast cancer treatment used ubiquitously to treat all stages of the disease, ductal carcinoma in situ, and as a pioneering chemopreventive. No other cancer drug has achieved this status. But with the description of SERMs in the 1980's, a whole new era in women's health was born. This is that story which will in the future encompass all members of the nuclear receptor superfamily.

Discovery of Nonsteroidal Antiestrogens

The discovery of the antiestrogenic properties of MER25 (ethamoxytriphetol) (Fig. 1) (1) was in part chance but an example of serendipity ie: an unanticipated advance in knowledge. Dr. Leonard Lerner was a young reproductive endocrinologist at the William S. Merrell Company in Cincinnati in the mid 1950's, charged with the investigation of nonsteroidal estrogens for clinical applications. Lerner was glancing through compounds to be tested in the cardiovascular program and notice that one MER25 had a structure resembling triphenylethylene-like estrogens. He asked for the compound to test but unexpectedly he found no estrogen-like activity in any species tested (3). Instead he noted weak but consistent antiestrogenic action in all animal models (1). The compound was also structurally similar to triparanol (Fig. 1), a drug originally marketed by the Merrell Company to reduce circulating cholesterol levels, but was withdrawn because triparanol increases circulating desmosterol levels (Fig. 2) which was thought to be responsible for the rapid onset of cataracts in young women (4, 5).These observations were to be essential for

the future drug development of nonsteroidal antiestrogens when they would eventually be required to be given for up to a decade (6).

Clinical trials with MER25 were conducted (3) but not reported in the literature. By contrast, clinical trials with clomiphene (Fig. 1), a mixture of estrogenic and antiestrogenic geometric isomers of a triphenylethylene was tested extensively for the regulation of fertility but shown to induce ovulating in subfertile women (2) and showed modest activity as a breast cancer therapy (7). However, the breast cancer treatment option was discontinued as clomiphene produces an increase in desmosterol Fig. 2.

The Upjohn Company focused a huge synthetic effort on the antifertility properties of indene and naphthalene (8) derivatives thereby solving the issue of separating the isomers of triphenylethylenes, the landscape of which had actually been defensively patented by Merrell in the 1960's. The Upjohn Company discovered a compound, U-11, 100A (Fig. 1) that would be unsuccessfully developed as a breast cancer drug (9). The compound, renamed nafoxidine was effective at controlling the growth of 30% of breast cancers for about a year but severe side effects such as photophobia precluded further clinical development. Nevertheless, nafoxidine was the structural basis for a new SERM lasofoxifene examined 20 years later (see last section). The fact that Merrell defensively patented triphenylethylenes as breast cancer drugs prevented patent security for tamoxifen in the United States until 1985 of their original patent submitted in the 1960's! The defensive patenting of triphenylethylenes by Merrell was actually to turn out to be a stimulus for innovation in medicinal chemistry and after 1985 was to create a significant unanticipated financial windfall for ICI Pharmaceuticals Division that had now undergone a metamorphosis to Zeneca. In 1984, an NCI panel declared long term adjuvant tamoxifen therapy the antihormone treatment of choice for the treatment of ER positive breast cancer (10) and Zeneca now had 20 years patent protection. This provided profits to invest in chemoprevention and fund the development of a range of other leading and innovative antihormonal therapies: bicalutamide, anastrozole, and fulvestrent at Zeneca.

The patenting restrictions led Eli Lilly to explore chemistry described originally in India at the Central Drug Research Institute in Lucknow, India (11) to link the bulky antiestrogenic group by a ketone bridge to the ER ligand binding moiety (12). The result was trioxifene (Fig. 1) that was to fail against tamoxifen in clinical trials to treat breast cancer. Nevertheless, the structural advance gave the world the high affinity antiestrogens LY117036 (13) and LY156,728 (14) after it was discovered that tamoxifen was metabolically activated to the high affinity antiestrogen 4-hydroxytamoxifen (15, 16). During the late 1960's and throughout the 1970's tamoxifen was being developed glacially throughout the world (including the United States without patent protection) by ICI Pharmaceuticals Division. Why was that and how did the opportunity to change that, significantly advance women's health?

The Tamoxifen Tale

During the early years of the 1960's, Arthur Walpole, Mike Harper, and Dora Richardson were the key members of the Fertility Control program at ICI Pharmaceuticals Division,

Alderley Park, near Macclesfield, Chesire. Walpole was the senior scientist and head of the program, Harper was the experimental reproductive endocrinologist and Richardson the synthetic organic chemist. The team was tasked with advancing the goal of discovering a safe and effective "post coital" contraceptive and the work on reproduction would be continued by Labhsetwar into the 1970's (17–20) despite the fact that the fertility program was going nowhere. The principal achievements of the team was the discovery that the geometric isomers of a substituted triphenylethylene were estrogenic or antiestrogenic: the cis isomer ICI 47,699 was an estrogen (21) and the trans isomer ICI 46,474 was an antiestrogen with antifertility properties in the rat by preventing implantation that was found to be an estrogen dependent process (22, 23). Most importantly, for the future development of ICI 46,474, as a long term anticancer agent, the antiestrogen did not increase desmosterol levels in rats (22).

Although Walpole had an interest in cancer research (24) no studies were conducted at ICI Pharmaceuticals Division but Walpole did initiate clinical studies outside the company to demonstrate activity as an anticancer agent in metastatic breast cancer (25, 26) and like clomiphene, the induction of ovulation in subfertile women (27). However, in the spring of 1972, a meeting was held at ICI Pharmaceuticals Division to review all clinical progress with ICI 46,474 and the decision was subsequently made to terminate clinical development. Fortunately for me (VCJ), and probably for my future career, Arthur Walpole was the examiner of my PhD on "failed contraceptives" entitled: *A Study of the Oestrogenic and Anti-oestrogenic Activities of Some Substituted Triphenylethylenes and Triphenylethanes*. I passed my PhD examination and I was appointed as a faculty member at Leeds University in mid-1972 but was required to obtain my "Been to America" (BTA). My chairman in the Pharmacology Department Mike Barrett (formerly of ICI Pharmaceuticals) and Walpole recommended I spend two years at the Worcester Foundation (the home of the oral contraceptive), with Mike Harper who was now heading a research team to develop a once-a-month pill. Mike Harper had published all of the antifertility properties of ICI46,474 in the mid 1960's (21–23) when he was at ICI Pharmaceuticals Division, Alderley Park.

When I (VCJ) got to the Foundation in September 1972, Harper had left to accept an appointment at the World Health Organization in Geneva and I was told I could do anything I wanted as long as some of it involved contraception. A phone call to Walpole at ICI Pharmaceuticals Division to discuss the idea that ICI 46,474 should be developed as a breast cancer drug, resulted in an unrestricted research grant to study the anticancer properties of ICI 46,474 in the laboratory, an appointment to be an ICI Americas consultant on the project and act as an advisor to them with clinical trial cooperative groups in America. What I did not know was that Walpole had tendered his resignation in 1972, but he agreed to remain at ICI Pharmaceuticals Division if ICI 46,474 was put on the market as an orphan drug. He suggested that funds be made available for me (VCJ) to discover the best strategy for the clinical use of ICI 46,474 as a breast cancer drug. ICI Americas/ICI Pharmaceuticals Division/and the Yorkshire Cancer Campaign would fund my (VCJ) laboratory first at the Worcester Foundation and then at Leeds University throughout the 1970's. That decade resulted in publications to support three strategic applications of tamoxifen (formerly ICI 46, 474): target the ER in the tumor where tamoxifen and its metabolites block estrogen

stimulated growth (15, 28), tamoxifen for the prevention of mammary carcinogenesis (29, 30) and the idea of long term adjuvant tamoxifen therapy would be the appropriate strategy to prevent tumor recurrence (31–33).

During the next 30 years, clinical studies established unequivocally that long term adjuvant tamoxifen therapy using 5 or more years of treatment produced major survival advantages for patients with as ER positive breast tumor (6, 34–36). However, it was the paradigm shift from treatment to chemoprevention during the 1980's and 1990's that opened up new opportunities in women's health.

The chemoprevention of breast cancer in high risk women

The idea that breast cancer can be prevented is not new. In 1936, Professor Antoine Lacassagne (37) presented the following strategy at the Annual Meeting of the American Association for Cancer Research in Boston.

> If one accepts the consideration of adenocarcinoma of the breast as the consequence of a special hereditary sensibility to the proliferative actions of oestrone, one is led to imagine a therapeutic preventative 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 antagonistic or excretory, to prevent the stagnation of oestrone in the ducts of the breast.

However, at that time there were no "antiestrogenic" compounds and neither was there a target at which to aim. The compounds were to develop from the serendipitous discovery of MER25 (38). The main compounds were all discovered and developed on the evidence of a bioassay in vivo: the inhibition of postcoital implantation in rodents! The target was to be discovered using high specific activity tritiated estrogen in whole animal distribution studies with the tritiated estrogen binding in and being retained in estrogen target tissues ie: uterus, vagina, pituitary gland (39, 40). The ER was first identified as an extractable protein from immature rat uteri (41, 42). From there, translation to clinical applications in breast cancer flowed with the ER assay to determine estrogen dependent growth in breast tumors as a predictive test for ablative surgery in advanced disease (43) and then transformed into a target for antiestrogen action to treat breast cancer (44).

In 1986, Professor Trevor Powles took the initiative to be the first recruit a vanguard study of high risk women for what was to become the "Royal Marsden Study". He based his plan on the fact that tamoxifen prevented rat mammary carcinogenesis (29, 30, 45) and adjuvant tamoxifen reduced the risk of contralateral breast cancer (46). His early results (47) proved provocative as there was maintained compliance vs. placebo but the spectre of carcinogenesis with tamoxifen was already apparent and this had to be addressed in any future trials. Nevertheless, substantial recruitment and compliance continued and a decrease in breast cancer incidence was noted at a 20 year follow-up (48). It was clear from studies in athymic mice with transplantable ER positive tumors, that a target site specificity with tamoxifen was occurring. Since Harper and Walpole's (21, 22) first publications on ICI 46,474, there was known species specificity; tamoxifen was classified as an antiestrogen in

the immature rat uterus but an estrogen in the ovariectomized mouse uterus and vagina. However, studies of metabolic differences did not prove the obvious – tamoxifen was an estrogen in the mouse because it is metabolized to an estrogen (49). Studies in the athymic mouse were to demonstrate that tamoxifen did not support the growth of ER+ MCF-7 tumors but stimulated the uterus to grow (50). It was stated “these studies strongly support the concept that the drug (tamoxifen) can selectively stimulate or inhibit events in target in tissues of different species without metabolic intervention”. “The drug-estrogen receptor complex is perceived as a stimulatory or inhibitory signal”(50). Subsequent studies in the high incidence mammary tumor strain of mice (C3HOUJ) demonstrated that tamoxifen prevented mammary tumor carcinogenesis and was superior to oophorectomy (51). The original prediction by Lacassagne was correct (37). Nevertheless, the “breakthrough” experiment that had major ramifications for clinical medicine and patient care was the finding that athymic mice bitransplanted with an ER positive breast tumor (MCF-7) and an ER positive endometrial cancer (EnCa 101) would exhibit “antiestrogenic” actions on the breast tumor to stop growth but “estrogenic” action in the endometrial cancer to promote growth (52) (Fig. 3). These data were presented to the clinical community (53, 54) with the concern “a large cohort of patients under long term tamoxifen therapy (>5 years) needs to be monitored for the occurrence of tamoxifen-stimulated endometrial tumors” (52).

Retrospective analysis of clinical trials data confirmed there was a low but significant increase in endometrial cancer incidence in postmenopausal women receiving long term adjuvant tamoxifen treatment (55, 56). Not only was this finding important for patient care in general practice but also this knowledge was essential to ensure safety for the trials that were planned to test the worth of tamoxifen to prevent breast cancer in high risk women (57–59). However, the surprise was the toxicological finding that high dose tamoxifen treatment for the life-time of a rat would initiate hepatocellular carcinoma (60–62). Fortunately these data did not translate to clinical practice. The Oxford Overview of clinical trials did not show an increase in hepatocellular carcinoma in patients receiving adjuvant therapy but it is clear that if tamoxifen had been tested for carcinogeneity in 1973 when the first animal studies for adjuvant therapy and chemoprevention were started, tamoxifen would not have been developed by the pharmaceutical industry (63). Hundreds of thousands of women would have died and the aromatase inhibitors would have been abandoned as these new antihormonal agents were only developed because the strategy of long term adjuvant tamoxifen was shown to be successful financially (63)!

This is not the place to review the results of the tamoxifen trials of chemoprevention. Suffice to say they were successful overall (48, 57–59, 64, 65) and tamoxifen was approved by the FDA in 1998 as the pioneer for the reduction of breast cancer incidence in pre and postmenopausal women with a high risk.

What is important to stress is the fact that a more transparent understanding of tamoxifen’s pharmacology and long term safety was needed in the 80’s if tamoxifen was to advance in the 90’s for broad clinical testing as a chemopreventive. The question was straight forward: “if tamoxifen is classified as an antiestrogen but estrogen is necessary to maintain bone density and (as was thought at the time) to decrease the risk of coronary heart disease, what advantage would there be in preventing half a dozen breast cancers per 1000 women per

year if 300 women developed osteoporosis and there were more women dying of heart attacks?" Unexpectedly, a series of laboratory studies was to provide reassurances that tamoxifen was not "just an antiestrogen" but it was selectively estrogenic and antiestrogenic in different estrogen target tissues around a woman's body. Most importantly, the laboratory finding all translated to successful clinical trials and a new paradigm was conceived with the creation of a new group of medicines – the Selective Estrogen Receptor Modulators or SERMs.

Nonsteroidal antiestrogens were "born" but SERMs were "conceived"

Nonsteroidal antiestrogens had initially been developed and failed in their primary application as "morning after" pills but in the 1960's and 70's both clomiphene and tamoxifen succeed in a secondary application. The fact that subfertile women could now induce ovulation and successfully give birth to children was a pioneering advance but not, at that time, a significant market. Another secondary application was the treatment of metastatic breast cancer, but this too was an insignificant market for a palliative drug such as tamoxifen. By contrast, what happened over 30 years was the confirmation that long term adjuvant tamoxifen therapy was the best strategy for clinical trials (66) and would be found to save perhaps millions of lives. The FDA approval of tamoxifen for chemoprevention in 1998 would now result in another blockbuster drug resurrected through the development of the new and novel strategy (38) of using a SERM (raloxifene) to prevent multiple diseases in women.

Serendipity took control with an initial investigation of the effects of tamoxifen and a failed breast cancer drug keoxifene on ovarectomized rat bone loss (67). The findings were not anticipated; what was anticipated was that these two nonsteroidal antiestrogens would increase bone loss. What was found was that the opposite occurred and that ovarectomized rats treated with the antiestrogen plus estrogen had no bone loss. By contrast, the antiestrogens blocked estrogen induced increases in uterine weight (67). There was target site specificity for nonsteroidal antiestrogens. This was not unlike the estrogen-like effects of tamoxifen in the athymic mouse uterus vs the prevention of estrogen stimulated growth of an implanted breast tumor (50) or the stimulation of endometrial cancer growth against the inhibition of growth of a breast tumor implanted in the same athymic mouse (52). All results had been observed at the same time in our Tamoxifen Team laboratory in Wisconsin – it was a principle! This was the preliminary data used to fund and advance subsequently successful clinical trials (68–70). With this knowledge, and the fact that tamoxifen caused a decrease in circulating cholesterol in rats (Fig. 2) (22) which, incidentally, caused ICI Pharmaceuticals Division to place a "hypocholesterolanemic" indication in their patent application 20 years earlier (71), it was now possible to consider a new approach to preventing breast cancer by developing multifunctional medicines for women's health. This was a prescient concept because the carcinogenic problems with tamoxifen, once they surfaced, (55, 61) would not go away and would preclude broad applications for the medicine in women's health. The new concept (38) was stated simply and directly based on laboratory data ie: before the publication of the results of ongoing clinical trials at the time with tamoxifen or initiation of new trials with other SERMs, as a roadmap for the pharmaceutical industry to follow.

> Is this the end of the possible applications for antioestrogens? Certainly not. We have obtained valuable clinical information about this group of drugs that can be applied in other disease states. Research does not travel in straight lines and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous application of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be post-menopausal women in general, thereby avoiding the requirement to select a high risk group to prevent breast cancer.

Raloxifene (Fig. 1) was the result. It was actually the obvious choice (the compound had been tested clinically previously and was a failed breast cancer treatment under its former name keoxifene) as it was now known to preserve bone density in the laboratory (67), prevent carcinogen induced mammary cancer in rats (72), be less uterotrophic then tamoxifen in rats (14, 73, 74) and inhibit tamoxifen stimulated endometrial cancer growth (75). These findings were subsequently confirmed by others in the laboratory (76), in clinical trials for osteoporosis (77, 78) and trials to evaluate the reduction of risk in breast cancer in high risk postmenopausal women (79, 80). Raloxifene is now FDA approved for the treatment and prevention of osteoporosis and the chemoprevention of breast cancer in postmenopausal high risk women. The SERMs had travelled from concept (38, 81) to a clinically proven “cluster”, of medicines: tamoxifen (and the related compound toremifene – a safer SERM in rats (62) but used to treat breast cancer(82)) and raloxifene that succeeded despite their original development plan as a breast cancer drug which failed. It has taken about 15 years of clinical gestation since tamoxifen (breast cancer risk reduction) and raloxifene (prevention of osteoporosis) were FDA approved for use in women at risk for disease but there has been a recent flurry of SERM approvals that deserve special comment. The new SERMs are innovative reinventions of early molecules in medicinal chemistry as the science has become more sophisticated and novel target for improvements in women’s health more imaginative.

New developments

Current progress in the FDA approvals of the new SERMs bazedoxifene (Fig. 4) for the prevention of osteoporosis and (in combination with conjugated estrogen) for the amelioration of postmenopausal hot flashes and ospemiphene (Fig. 4) for the improvement of atrophic vaginal symptoms and vaginal lubrication has been presented earlier (83, 84). The summary of FDA approved SERMs to enhance and cement the market are illustrated in Fig. 4 but the figure also includes lasofoxifene that was approved in the European Union but with no plans for launching the product for the treatment and prevention of osteoporosis. Approval has lapsed. Despite this deficit, the medicine is worthy of comment because of the advance in pharmacology as a multifunctional medicine in women health.

Bazedoxifene, ospemifene, and lasofoxifene each are compounds derived from prior pharmalogical knowledge (Fig. 5). The principal structural feature of basedoxifene that

binds to the ER is a potential metabolite of a failed breast cancer drug called zindoxifene that was found to actually be an estrogen (85). The core ligand was married to a predictable bulky antiestrogenic side chain to create the new SERM bazedoxifene (86). Ospemiphene is a known metabolite of the SERM toremifene (82) that was studied in detail twenty years ago when tamoxifen was found to have the potential to be carcinogenic in rat liver at high doses (62). It seems that tamoxifen is hydroxylated in the α position on the ethyl substitution at the ethylene bond and this is the metabolite that caused adduct formation in the rat liver DNA. Toremifene has a β chlorine so α hydroxylation does not occur (62) and it is a safer SERM in rat liver. However, this metabolic transformation has no toxicological relevance in patients. The “antiestrogenic” side chain of ospemiphene is a glycol formed by the deamination of the dealkylated toremifene side chain. This metabolic transformation was first noted for tamoxifen (87, 88) in patient sera and the metabolite, metabolite Y was confirmed as a weakly antiestrogenic compound with partial estrogen-like actions (88).

We have met the origins of lasofoxifene earlier. It is the compound U-11,100A or nafoxidine (Fig. 1), discovered at the Upjohn research laboratories in their search for antifertility agents (8) but developed as a potential breast cancer drug that failed because of severe toxicities (9). Lasofoxifene (Fig. 5) is a miracle of medicinal chemistry. With demethylation of nafoxidine, the resulting molecule has high affinity for the ER but as a result, the molecule also has rapid clearance because of phase II metabolism and increased excretion. This principle was first illustrated by 4-hydroxytamoxifen (15, 16, 32) and noted in raloxifene analogs (74). However, reduction of the lone double bond in the non-aromatic ring of nafoxidine results in a possibility of two diasterioisomers. One isomer is used that is protected from conjugation and phase II metabolism. As a result lasofoxifene is used at a daily dose of 0.5mg for the treatment and prevention of osteoporosis (89). This contrasts with raloxifene used at a 60mg daily dose either for the treatment and prevention of osteoporosis or the prevention of breast cancer (77, 79, 90).

Once the SERM concept was conceived (38, 81) clinical development advanced effectively with raloxifene as the molecule was known to be free from endometrial cancer in animals and did not produce rat liver carcinogenesis. The drug would be safely used for the prevention of osteoporosis in otherwise healthy women! However, despite the fact raloxifene reduces cholesterol levels in rats (76), there was no evidence of any benefit by a reduction of coronary heart disease in high risk women (91). However, tamoxifen and raloxifene were both two “repurposed” drugs (92) and there was still a long way to go to discover the “ideal SERM” as a multifunctional medicine (Fig 6). Lasofoxifene, the nafoxidine derivative, was to produce a few surprises. The PEARL trial of lasofoxifene in postmenopausal women at risk for osteoporosis used 0.25mg and 0.5mg daily doses against a placebo control to determine the prevention of osteoporosis (89). Fractures were decreased, and breast cancer incidence was also reduced (93). The surprise was a decrease in coronary heart disease and also a decrease in strokes (89). The incidence of endometrial cancer was not increased but there was an estrogen-like increase in deep vein thrombosis. Lasofoxifene has demonstrated that medicinal chemistry and a commitment to large well organized clinical trial can provide much valuable information about the potential of selective modulation of the nuclear receptor superfamily.

If there is a message from the past 40 years of drug discovery, it is that a failure in one application can be a discovery in another (38). There were a lot of "failures" but translational research was advanced to benefit women's health. In the closing years of the 19th century, the French author Jules Verne wrote: *whatever one man is capable of conceiving, other men are capable of achieving.* The SERMs were *conceived* (38) based on a cluster of interlocking experiments conducted by the Tamoxifen Team at the University of Wisconsin Comprehensive Cancer Center (1980–1993) (49–52, 67, 72–74, 85, 87, 88, 94). A more detailed survey of SERMs and their origins for women's health can be found elsewhere (95, 96). Today, this particular special issue of STEROIDS provides opportunities for the next generation of men and women medical scientists to achieve success in their professional careers with the discovery of new modulating medicines in human health targeting the nuclear receptor superfamily.

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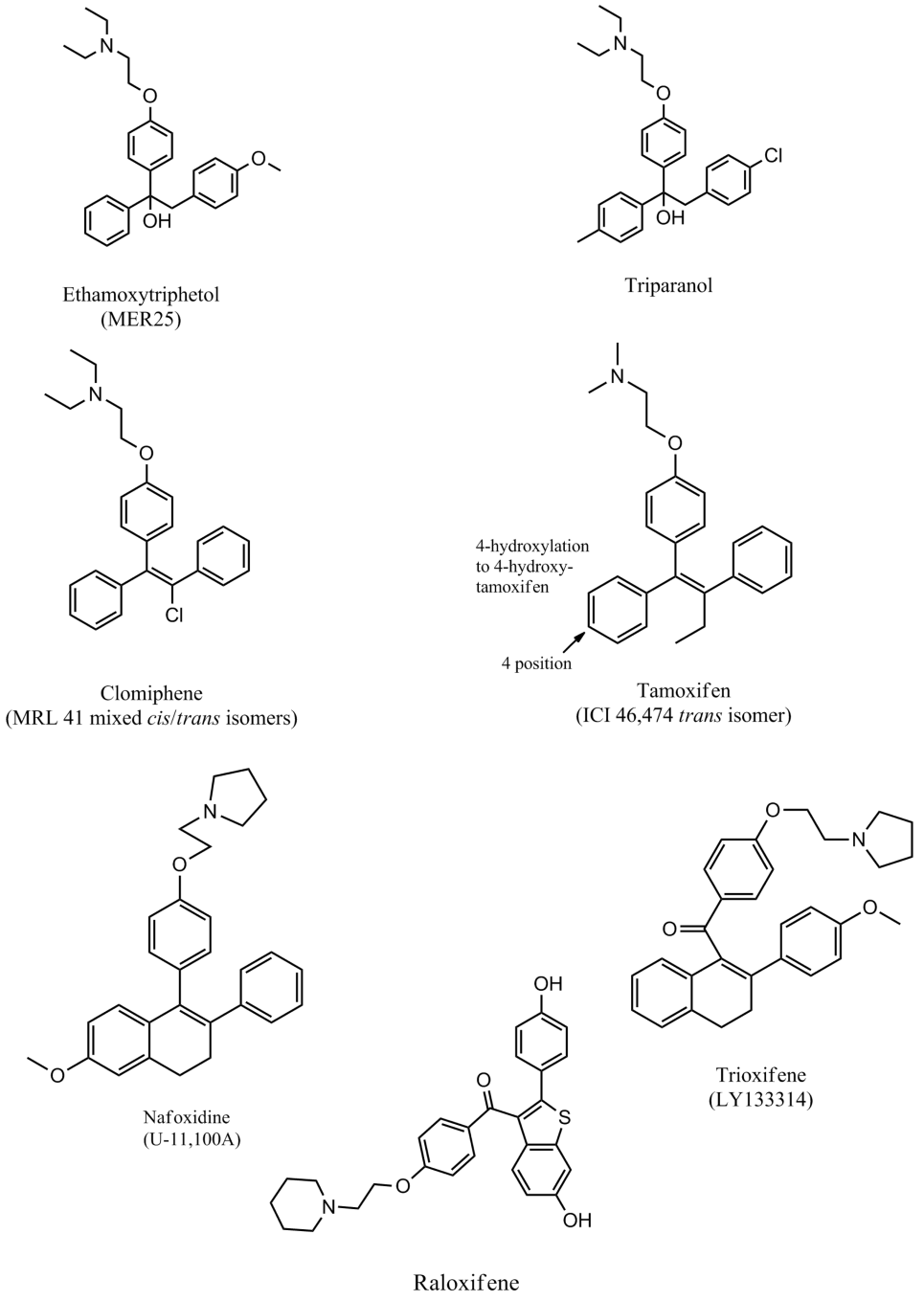

Fig. 1.
Compounds described in the text.

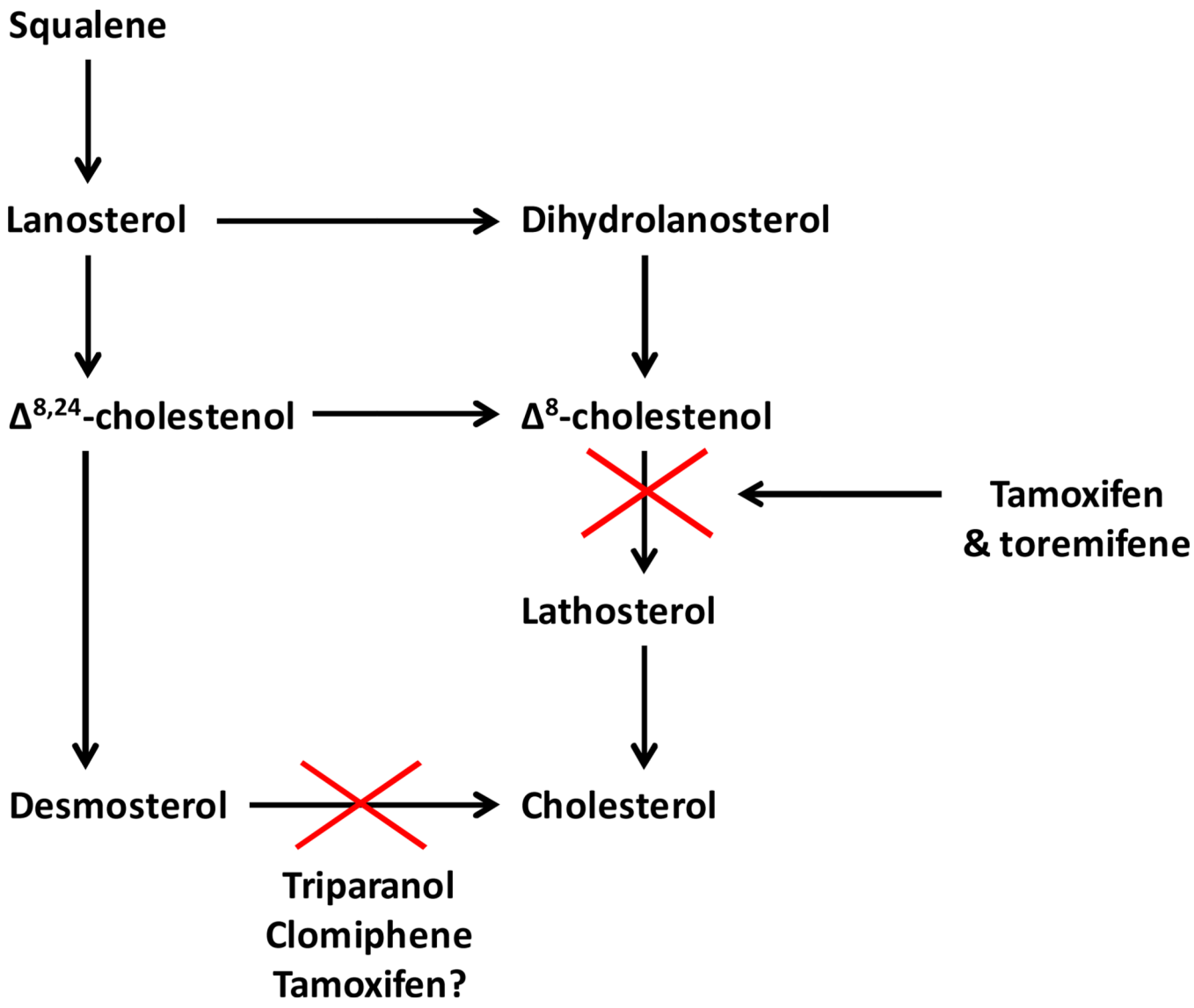

Fig. 2.

The inhibition of cholesterol biosynthesis by triparanol, clomiphene, tamoxifen, and the β-chlorinated derivative of tamoxifen toremifene.

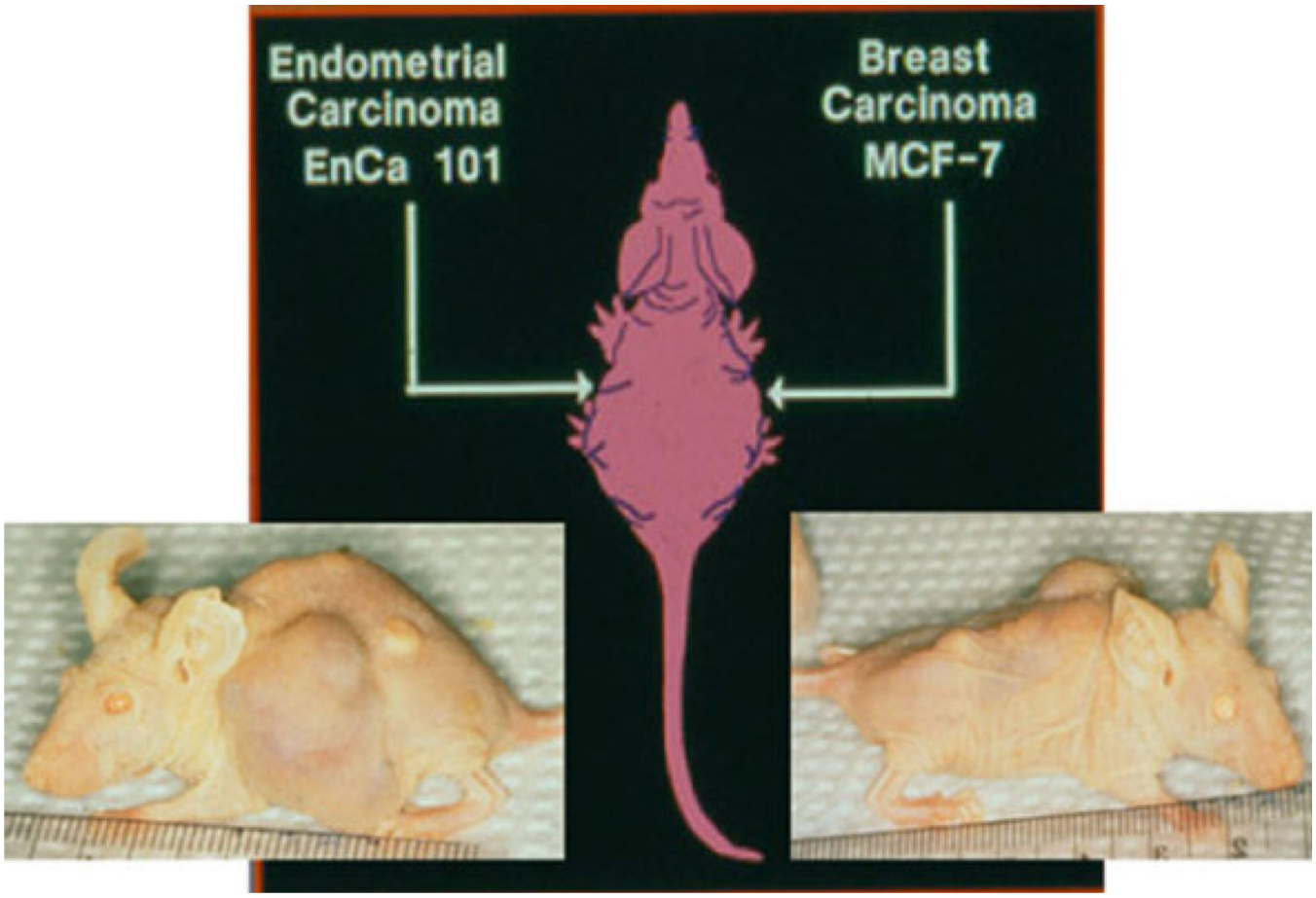

Fig. 3.

The pioneering bitransplantation study by Gottardis (72) with an ER-positive breast tumor (MCF-7) implanted in one axilla and an ER-positive endometrial tumor (EnCa 101) in the other axilla. Tamoxifen blocks estrogen-stimulated growth of the breast tumor (right), but tamoxifen encourages the growth of the endometrial tumor (left). These data were transmitted immediately to the clinical community (53, 54), confirmed in clinical trials (55, 56) to change clinical practice.

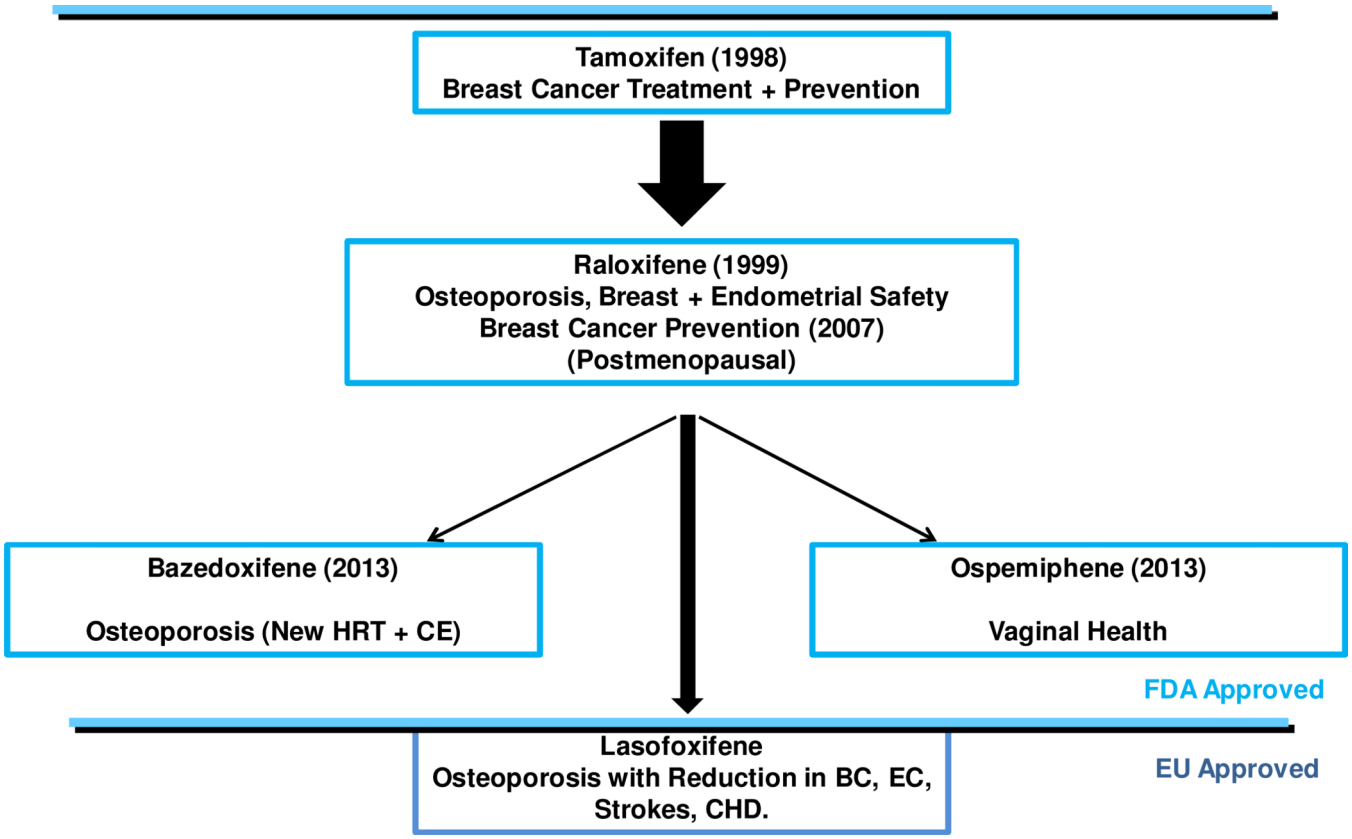

Fig. 4.

The approvals of individual selective oestrogens receptor modulators (SERMs) in the United States of America through the evaluation system of the Food and Drug Administration (FDA). Approvals were specifically for indications at the highest level of toxicologic safety for women without disease but as a new hormone replacement therapy with conjugated estrogen (HRT+CE) to prevent disease ie: chemoprevention of osteoporosis, breast cancer (BC), menopausal symptoms or dyspareunia. One SERM, lasofoxifene, was approved for use in the European Union (EU) but was never launched or marketed despite the fact that clinical trials demonstrated a reduction in breast cancer (BC), osteoporosis fracture, strokes, endometrial cancer (EC) and coronary heart disease (CHD) (89).

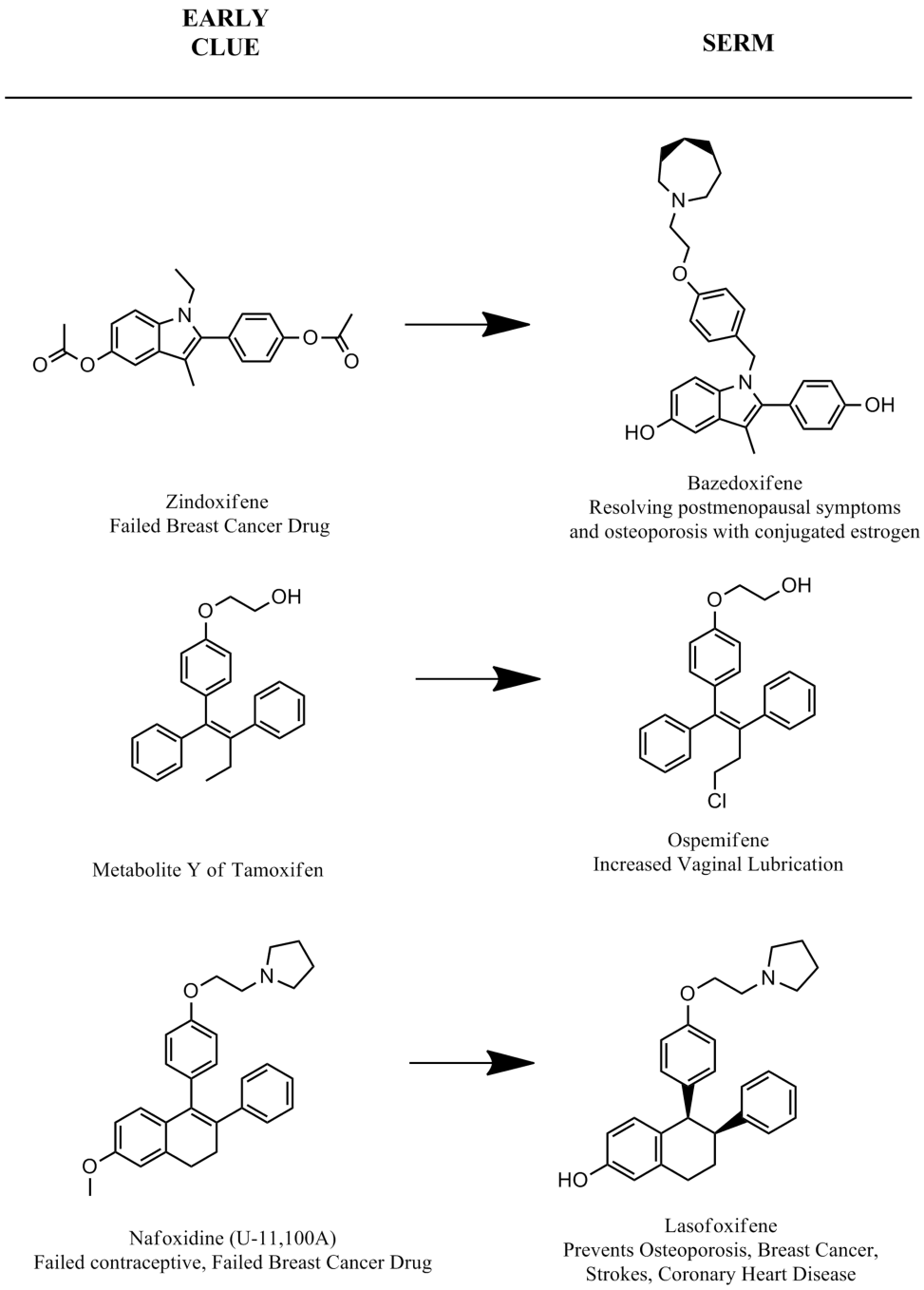

Fig. 5.

Origins of current selective ER modulators from earlier nonsteroidal antiestrogens. The discovery that the metabolite of tamoxifen, 4-hydroxytamoxifen (Fig. 1) has a very high binding affinity for the ER (15) acted as a catalyst for the design of the majority of future SERMs. The raloxifene drug development “odyssey” throughout the 1980’s (97) is a replay of the tamoxifen tale (71). During the 70’s (71), interestingly enough the work was done in the same laboratory but on different continents! The repurposing (92) and repatenting (97) of a failed breast cancer drug (keoxifene) resulted in raloxifene (Fig. 1), the same SERM, to

establish a principle in translational research. Bazedoxifene is an adaptation of an estrogenic metabolite from a failed breast cancer drug Zindoxifene (85). Ospemifene is a known metabolite of the breast cancer drug toremifene. The metabolite of toremifene was found because an analogous metabolite Y was discovered for tamoxifen in the early 1980's (88). Lasofoxifene has its origins with failed antifertility agent discovered in the early 1960's U-11, 100A (8). The compound renamed nafoxidine was tested as a drug for the treatment of breast cancer but again failed because of serious side effects (9).

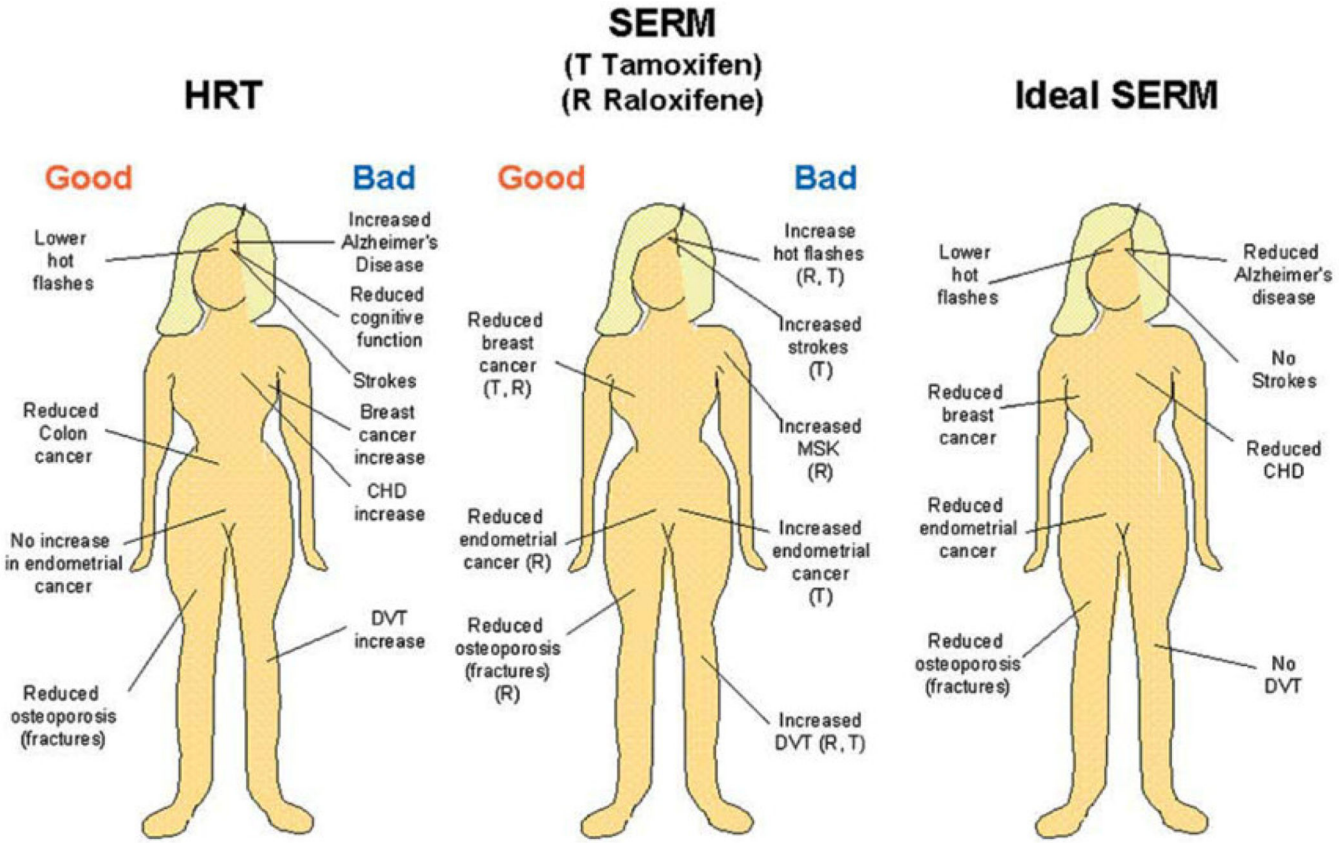

Fig. 6.

Progress toward an ideal SERM. The overall good or bad aspects of administering hormone replacement therapy (HRT) to postmenopausal women compared with the observed site-specific actions of the SERMs tamoxifen and raloxifene. The known beneficial or negative actions of SERMs have opened the door for drug discovery to create the ideal SERM or targeted SERMs to either improve quality of life or prevent diseases associated with aging in women. This figure is published with permission from Elsevier. Jordan, V.C. Selective estrogen receptor modulation: Concept and consequences in cancer. Cancer Cell, 2004 Mar; 5(3): 207–213.