available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Tamoxifen: Catalyst for the change to targeted therapy

*V. Craig Jordan**

Alfred G. Knudson Chair of Cancer Research, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, United States

ARTICLE INFO

Article history:
Received 30 October 2007
Accepted 2 November 2007

Keywords:
Breast cancer
Chemoprevention
Antioestrogen
Tamoxifen
Raloxifene
Selective oestrogen receptor modulator

ABSTRACT

In the early 1970s, a failed post-coital contraceptive, ICI 46,474, was reinvented as tamoxifen, the first targeted therapy for breast cancer. A cluster of papers published in the European Journal of Cancer described the idea of targeting tamoxifen to patients with oestrogen receptor positive tumours, and proposed the strategic value of using long-term tamoxifen therapy in an adjuvant setting with a consideration of the antitumour properties of the hydroxylated metabolites of tamoxifen. At the time, these laboratory results were slow to be embraced by the clinical community. Today, it is estimated that hundreds of thousands of breast cancer patients are alive today because of targeted long-term adjuvant tamoxifen therapy. Additionally, the first laboratory studies for the use of tamoxifen as a chemopreventive were published. Eventually, the worth of tamoxifen was tested as a chemopreventive and the drug is now known to have an excellent risk benefit ratio in high risk pre-menopausal women. Overall, the rigorous investigation of the pharmacology of tamoxifen facilitated tamoxifen's ubiquitous use for the targeted treatment of breast cancer, chemoprevention and pioneered the exploration of selective oestrogen receptor modulators (SERMs). This new concept subsequently heralded the development of raloxifene, a failed breast cancer drug, for the prevention of osteoporosis and breast cancer without the troublesome side-effect of endometrial cancer noted in post-menopausal women who take tamoxifen. Currently, the pharmaceutical industry is exploiting the SERM concept for all members of the nuclear receptor superfamily so that medicines can now be developed for diseases once thought impossible.

1. Introduction

A new dynasty gives dominion over the ruling dynasty through perseverance and not by sudden action (Ibn Khaldun 14th Century Arab Historian) – and so it is with changes in the approach to cancer therapy. This article will focus specifically on a cluster of scientific papers[1–3] published in the European Journal of Cancer that presaged the dramatic changes that have occurred in the past 35 years in our approach to cancer therapy. To set the scene, it is first appropriate to describe the research and treatment philosophy for breast cancer before tamoxifen.

In the 1960s, the use of combination cytotoxic chemotherapy for the treatment of breast cancer had moved to centre stage in the wake of an abstract presented at the American Association for Cancer Research.[4] The cytotoxic 'cocktail' presented by Cooper, containing cyclophosphamide, methotrexate, 5 fluorouracil, vincristine and prednisone (CMFVP), produced a dramatic response rate of >80% in patients with advanced breast cancer. In the 1960s, there was every reason to believe that cancer would be curable if (1) the right drug combination could be found; (2) the patient could be kept alive through the aggressive high dose regimens; and (3) pa-

* Tel.: +1 215 728 7410; fax: +1 215 728 7034.
E-mail address: v.craig.jordan@fccc.edu
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.11.002

tients could be treated with a low tumour burden. Cytotoxic chemotherapy became king and a new dynasty was established with the initiation of a lexicon of drug combinations and schedules and ultimately, bone marrow transplantation. The introduction of adjuvant therapy, as it turned out, would be essential for the successes we see today when the move occurred from cytotoxic chemotherapy to tamoxifen treatment. The initial hypothesis for the use of cytotoxic chemotherapy was reasonable and logical; adjuvant chemotherapy would destroy undetected micrometastases harboured around the patient's body after surgical removal of the primary tumour. The perfect result would be enhanced cures for women with breast cancer but the biology of breast cancer conspired to defeat the best attempts of oncologists to deploy non-specific cytotoxic chemotherapy effectively. The hypothesis was flawed.

It is the responsibility of each new generation to challenge the fashions in medicine created by the ruling dynasty. Progress by defying the dynasty can be profound and today we witness the results of an unlikely revolution in thinking that had its roots in the 1970s. Around the world, death rates from breast cancer are declining and patients are living longer, recurrence-free lives with less morbidity. Tamoxifen is an integral reason for current progress, but this was unanticipated in the 1970s. Thirty-five years ago it would have been unthinkable to suggest that 'hormone therapy' would enhance survivorship and that breast cancer risk reduction would now be a clinical reality.

Our knowledge of human oncogenes, an unknown idea in 1972 (C-src the first oncogene was described in 1976) now provides invaluable clues to exploit, selectively, the metabolic vulnerabilities in cancer. This knowledge is creating justifiable optimism by targeting the disease specifically with new agents. The current generation has witnessed the clinical (and economic!) success of agents like trastuzumab that targets gene amplified HER2-neu[5] in select breast cancers to produce disease control[6–8] not previously thought possible. However, the new era of individualised targeted medicines that promises 'to kill or prevent the cancer but not harm the patient' did not start with biotechnology.

The origins of targeted therapy started in the 1970s by challenging cytotoxic chemotherapy with an alternative approach to treatment which was achieved by adapting the pharmacological principles of drug receptor theory to cancer care. At that time, cancer research was considered to be a hopeless career choice, but a series of events put the right people in the right place at the right time to recognise a unique opportunity to advance cancer therapeutics. No advances occur in isolation; they build on the work of previous generations and in this case, by collegial interaction.

2. Tamoxifen (ICI 46,474) before targeting

ICI 46,474, the antioestrogenic *trans* isomer of a substituted triphenylethylene, was discovered in the laboratories of Imperial Chemical Industries (ICI) Ltd. Pharmaceuticals Division (now AstraZeneca). The team, Dora Richardson (Chemist), Michael J.K. Harper (Reproductive Endocrinologist) and Arthur L. Walpole (Head of Reproduction Research) was tasked with developing a post-coital contraceptive during the early 1960s based on the structural clues already published by other pharmaceutical companies. All of the studies conducted at ICI throughout the 1960s were focused on reproduction and the patent issued throughout the world (except the United States where the patent was denied for 20 years because the findings did not demonstrate innovation) stated '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 tumours or for the management of the sexual cycle and aberrations thereof. They also have useful hypocholesteraemic activity'. Claims that the compounds could be used as a breast cancer treatment had to be removed from the patent applications in America as they were considered to be fantastic![9] More importantly, there was no evidence to back up the claim.

Walpole was not only interested in reproductive endocrinology but also cancer research and treatment.[10] The scientists at ICI had found an unusual species specificity with ICI 46,474; the compound was apparently a classical oestrogen in the mouse vagina but an antioestrogen in rat tests.[11,12] The question was what was the pharmacology of ICI 46,474 in humans: an oestrogen or an antioestrogen? Walpole advanced clinical testing of ICI 46,474 in both 'the control of hormone dependent tumours' and 'the regulation of the sexual cycle'. Clinical testing was initiated to evaluate activity to treat breast cancer at the Christie Hospital in Manchester and the Princess Margaret Hospital, Birmingham[13,14] and reproductive cycle studies proceeded elsewhere.[15] In 1972, all conclusions were reviewed by ICI Ltd. Pharmaceuticals Division in Alderley Park, Macclesfield, Cheshire. Unlike the results observed in the rat, ICI 46,474[16] was not a contraceptive in humans. The drug induced ovulation and could potentially be used as a profertility agent.[15] ICI 46,474 exhibited modest activity as a breast cancer therapy which was equivalent to historical controls treated with high dose oestrogens or androgens.[13] The advantage of tamoxifen, that was to be critical for future applications, was a low incidence of toxic side-effects. However, the decision by senior management was to abandon further development,[9,17] primarily because the financial return for co-marketing a breast cancer drug used by a limited number of patients for about a year for the palliation of metastatic breast cancer was too small and there was virtually no market for another agent to induce ovulation in subfertile women. Clomiphene was already the medicine of choice.[18]

Walpole responded by electing to take early retirement if ICI 46,474 did not get marketed. He was at the end of his scientific career and he truly believed that tamoxifen had promise if only further studies could be completed on the 'orphan drug'. But how would this occur? Walpole and I met in September, 1972, when he was the external examiner of my PhD entitled 'Structure function relationships of some triphenylethylenes and triphenylethanes' at the University of Leeds. Following this meeting, Walpole provided resources for me to conduct the scientific work that reinvented a failed contraceptive to become the first targeted therapy for the treatment and prevention of breast cancer. We collaborated until his untimely death in 1977.[10]

3. Foundations

In 1969, I was seduced by the idea of crystallising the oestrogen receptor (OER) with an oestrogen and a non-steroidal antioestrogen. My supervisor thought it would be a little uninteresting, but at least the project would be straightforward as Leeds had a premier X-ray crystallography department called the Astbury Department of Biophysics. The OER protein could be easily extracted from uteri,[19,20] but I quickly found that purification was not a simple task. I switched my PhD topic to study the pharmacology of non-steroidal antioestrogens. As it turned out, this was a good career choice as no one has yet succeeded in crystallising the whole liganded OER!

I wanted to develop drugs for cancer, but there were no opportunities to pursue this goal during my PhD. What made life more complicated in 1972 was the fact that the University could not find anyone to be my external examiner; no one cared about the pharmacology of failed contraceptives! Although administrators at the University protested against the choice of someone from industry, Arthur Walpole was eventually appointed as my examiner; a fortunate event that was subsequently to advance the clinical application of tamoxifen by establishing a scientific foundation through an investigation of its antitumour actions in the laboratory.

During the final year of my PhD, I was invited to stay at Leeds as a lecturer in Pharmacology. However, first I was required to go to the Worcester Foundation for Experimental Biology (now the Worcester Foundation for Biomedical Research, part of the University of Massachusetts Medical School) to work with Michael Harper, Walpole's former colleague at ICI. When I arrived in September 1972, Harper declared that he had accepted a job at the World Health Organisation in Geneva and that 'I could do anything I wanted for the next two years'.

Here was the opportunity I wanted. A phone call to Walpole at ICI secured his enthusiastic financial support to re-examine ICI 46,474 in the laboratory, but this time the focus would be its mechanism of action as an anticancer agent. I was made a consultant to introduce ICI 46,474 to clinical trials groups in American and Lois Trench, the drug monitor for Stuart Pharmaceuticals (ICI Americas in Wilmington, Delaware) coordinated all administrative details between 1972 and 1974 to get the project off the ground. But how to start?

Elwood V. Jensen, Director of the Ben May Research Laboratory was on the scientific advisory board for the Worcester Foundation in 1972 (Fig. 1). During his visit in late 1972, we spent time going over my thesis and I explained what I wanted to do with ICI 46,474. He generously invited me to Chicago the next year to learn sucrose density gradient analysis in order to study whether tamoxifen blocked oestradiol binding to the human and animal OER. I also learned how to induce mammary tumours in rats using dimethylbenzanthracene (DMBA) so that the mechanism of antitumour action of tamoxifen could be evaluated under controlled laboratory conditions. The DMBA model was the only model available at the time to study hormones and cancer. The work commenced at the Worcester Foundation in the summer of 1973 and by the end of the year, results were pouring out. Lois Trench secured human tumours for sucrose density gradient analysis, but I felt no pressure to publish as no one was really interested. Chemotherapy was king and no one anticipated that another 'hormone therapy' would be an advance. As a pharmacologist, I was just happy to be contributing to the development of an anticancer drug.

Fig. 1 – V. Craig Jordan and Elwood V. Jensen on the occasion of learning they were going to be the inaugural recipients of the Dorothy P. Landon/AACR Prize (2002) for Translational Research. This is the highest award presented by the AACR and recognised the seminal work for both of these scientists; Elwood Jensen identified OER as the mediator of oestrogen action in its target tissues and some breast tumours, and Craig Jordan's research that reinvented ICI 46,474 from being a failed contraceptive to the first targeted therapy for breast cancer as the drug tamoxifen.

Avoiding writing up my results could not last forever. Dr. Eliahu Caspi, a senior scientist at the Worcester Foundation, was directed to interview me to explore the possibility of me staying at the Worcester Foundation and not returning to Leeds. This was a surprise, but there was an even bigger surprise in store when he glared at me over his desk and announced 'that I did not have a CV because I had not any publications'. I announced I had not yet solved any problems so what was the point? And he proceeded to give me the best advice of my academic career up to that time. 'Tell them the story so far; each paper should take no longer than two weeks to write-up and link together a series of studies with a theme'. I have not stopped writing since; which brings me back to the three papers I eventually published in the European Journal of Cancer.[1–3]

4. Transition to targeting Tamoxifen (Jordan VC, Koerner S. Tamoxifen (ICI 46,474) and the human carcinoma 8S oestrogen receptor. Eur J Cancer 1975;11:205–6)

Lars Terenius published two important papers in the European Journal of Cancer that described the action of nafoxidine for the treatment of DMBA-induced rat mammary tumours[21] and the ability of the first non-steroidal antioestrogen MER 25[22] to prevent rat mammary carcinogenesis.[23] These studies demonstrated 'proof of principle' for the application of antioestrogens to treat breast cancer, but neither compound showed any promise in the clinic because of serious toxic side-effects.[24,25] In fact, this was the consistent story for all of the antioestrogens, except for tamoxifen.

ICI, 46,474 was examined systematically in my laboratory to explore mechanisms and applications that could be exploited in the clinic. These studies were supported by ICI with unrestricted funds, first at the Worcester Foundation (1972–1974) and subsequently at the University of Leeds as a University Joint/Research Scheme (1974–1979). Most importantly, ICI arranged for thousands of rats to be chauffeured from Alderley Park to Leeds so I could complete my work. Those free rats, as it turned out, would be worth their weight in gold with the billions of pounds of profits earned with tamoxifen! Simultaneously, Rob Nicholson, at the Tenovus Institute in Cardiff started to use tamoxifen as a laboratory tool to investigate oestrogen and antioestrogen action in the DMBA-induced rat mammary tumour model. Again, these studies were published in the European Journal of Cancer.[26–28]

The studies I conducted in the laboratory initially focused on the ER as a therapeutic target. The questions that were addressed were 'can tamoxifen block oestrogen binding?' and 'is tamoxifen the active agent?' ICI 46,474 has a very low binding affinity for the ER and we used sucrose density gradient analysis to provide the first consistent evidence that tamoxifen blocks the binding of oestradiol to the human breast and endometrial cancer 8S oestrogen receptor.[1] We focused specifically on the role of the OER in tamoxifen action during the mid 1970s so that there would be a better understanding of tamoxifen action in its target tissues, the mammary tumour and uterus.[29–34]

At this time, we also made the observation that hydroxylated metabolites played an important role in the antioestrogenic and antitumour actions of tamoxifen.[35,36] We concluded that it was an advantage, but not a requirement, for tamoxifen to be metabolically activated to 4-hydroxytamoxifen. As a result of these studies, 4-hydroxytamoxifen became the standard laboratory tool to study the molecular biology of antioestrogen action *in vitro* and in 1998 was used to crystallise the ligand binding domain of the OER with an antioestrogenic molecule.[37] The key to this accomplishment was that 4-hydroxytamoxifen has about a 100× higher binding affinity for the OER than tamoxifen.

5. Tamoxifen for prevention? (Jordan VC. Effect of tamoxifen (ICI 46,474) on initiation and growth of DMBA-induced rat mammary carcinoma. Eur J Cancer 1976;12:419–24)

In 1936, Profession Antoine Lacassagne suggested, based on his animal studies, that 'a therapeutic antagonist should be found to prevent the congestion of oestrone in the breast' so that breast cancer could be prevented.[38] Forty years later, the first experiment I was to complete with tamoxifen showed that just two injections of the 'antioestrogen' would almost completely prevent carcinogenesis in the rat mammary gland.[2,39] I concluded that the mechanism was most likely blocking oestrogen action at the level of the OER in the mammary tissue and nascent tumour. These and subsequent studies[40–42] provided the scientific foundation for the eventual examination of the worth of tamoxifen to prevent breast cancer in high risk pre- and post-menopausal women.[43–46] The key to tamoxifen's success in this application was a sustained duration of action and its ability to produce antitumour actions long after the therapy has stopped.[44,47]

6. Long-term adjuvant tamoxifen therapy (Jordan VC, Allen KE. Evaluation of the antitumour activity of the non-steroidal antioestrogen monohydroxytamoxifen in the DMBA-induced rat mammary carcinoma model. Eur J Cancer 1980;16:239–51)

In the 1970s, the initial clinical studies of tamoxifen were focused entirely on its application as a treatment for metastatic breast cancer. The efficacy of tamoxifen was the same as that of high dose oestrogen therapy (diethylstilboestrol 15 mg daily), but the advantage of tamoxifen was fewer serious side-effects.[13,48] The translation of the early laboratory findings with tamoxifen[1,2] to the treatment of advanced breast cancer showed an association between the efficacy of tamoxifen as an antitumour agent and OER status.[49] However, it was the transition from the use of tamoxifen as a palliative therapy to adjuvant therapy that was to have the greatest impact on survivorship and to establish tamoxifen as the gold standard for antihormonal therapy from 1980 to 2000.

The goal of adjuvant therapy is to destroy the micrometastases that have spread around the body at the time of primary surgery. Early results with chemotherapy were extremely promising[50,51] and some significant improvements were noted once the overview analysis of worldwide randomised clinical trials was analysed and published.[52] However, the use of tamoxifen in this application was less readily accepted

because of the belief that tamoxifen was only a palliative therapy. As a prelude to the application of tamoxifen as an adjuvant therapy, I introduced the antioestrogen first to the Eastern Cooperative Oncology Group (ECOG)[53,54] and subsequently to the National Surgical Breast and Bowel Project (NSABP).[55] Early adjuvant clinical trials selected one year of adjuvant therapy[56–60] because of the fact that tamoxifen was effective in unselected patients with advanced breast cancer for about one year and there was a sincere concern that longer therapy would induce pre-mature drug resistance. These beliefs were to change in the mid 1970s with the laboratory finding that long-term antihormonal therapy was more effective than short-term therapy.

Marc Lippman published an important paper in 1975 on the actions of tamoxifen in cell culture.[61] He demonstrated that oestradiol could reverse the action of tamoxifen to stop

Fig. 2 – 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 Nolvadez Adjuvant Trial Organization (NATO) 2-year adjuvant tamoxifen trial[95,96]; 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 randomised Scottish Trial of 5 years' adjuvant tamoxifen treatment versus control in the 1980s.[97] 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.[98]

cell replication and that tamoxifen could actually kill breast cancer cells at high concentrations. We decided to test the idea that tamoxifen was cytotoxic *in vivo* using the DMBA-induced rat mammary carcinoma model.

We reasoned that daily treatment with tamoxifen for a month in the rat would be equivalent to a year in a woman. Administration of DMBA (20 mg in 2 ml peanut oil po) to 50-day-old female Sprague–Dawley rats resulted in the development of multiple mammary tumours in all animals about 150 d later.[62] The experimental approach we used was to administer different daily doses of tamoxifen for a month starting one month after DMBA administration. This design was to allow carcinogenesis to proceed following DMBA administration so that we could assess the effectiveness of tamoxifen to destroy the microfoci of deranged cells in the mammary tissue. This was as close as one could get to an endocrine adjuvant model in the 1970s.

Tamoxifen was compared with 4-hydroxytamoxifen because we had found it was the most potent antioestrogen then known[31]; at least 10 times more potent than tamoxifen. We chose to test 4-hydroxytamoxifen because we anticipated that it would be a more potent antitumour agent than tamoxifen. To our surprise, not only was 4-hydroxytamoxifen not as effective as tamoxifen, but short-term tamoxifen was unable to 'cure' animals. High doses of tamoxifen were superior to low doses of tamoxifen in reducing tumour numbers and controlled tumour appearance, but all animals eventually developed at least one tumour. Clearly, there was a link between dose and anticancer action, but it was because higher doses were cleared from the body more slowly and not that the higher dose was more active. Tamoxifen was acting as a tumouristatic agent – the drug was effective as long as the drug was present to suppress tumour growth (Fig. 2).[3,63,64] We proved this concept experimentally by showing that antioestrogens were effective at controlling tumourigenesis as long as treatment was continued. Indeed, if tumours occurred during antioestrogen therapy, they would respond to a second antihormone therapy, in this case, oestrogen withdrawal following ovariectomy. We concluded '*It was clear that antioestrogens do not destroy all the foci of hormone dependent tumour cells and long courses of therapy or the use of antihormonal methods e.g. ovariectomy are essential to control tumour growth*'.[3] This notion lead to the idea that longer was going to be better as a strategy to employ for adjuvant tamoxifen therapy and provided a scientific foundation for the successful use of subsequent oestrogen deprivation, i.e. an aromatase inhibitor following 5 years of tamoxifen treatment.[65,66]

The overview analysis of randomised clinical trials that occurs about every five years at Oxford has really revolutionised clinical thinking. The publications summarise treatment progress through the clinical trials mechanism. The clinical proof that longer tamoxifen therapy is better than shorter tamoxifen therapy is most readily demonstrated in the OER positive pre-menopausal patients. One year of tamoxifen was ineffective, but 5 years produced a dramatic effect on disease-free survival and overall survival.[67] More importantly, tamoxifen produced a survival advantage for women, of a magnitude that would change the perception of endocrine agents as only palliative. The key to success was targeting women with the right tumour with the correct duration of treatment at the right stage.

7. Conclusion

What were the consequences of reinventing a failed contraceptive ICI46,474[16] to become tamoxifen, the first targeted agent for the treatment of breast cancer[9]? The laboratory strategy of targeting OER positive tumours[1] with long-term adjuvant therapy[3,64] ultimately resulted in the improved survivorship of hundreds of thousands of women [67,68] around the world. Indeed, the fact that tamoxifen is cheap and accessible to under-funded healthcare systems worldwide means that this form of targeted therapy continues to save lives. However, unlike the targeted therapies of today that usually have a single anticancer application, tamoxifen became the gold standard for the targeted therapy of all stages of breast cancer (including male breast cancer), the treatment of ductal carcinoma in situ,[69] a pioneering agent for the chemoprevention of breast cancer in high risk women[45,70,71] and the lead compound for the new drug group, the SERMs.[72–76]

The extensive laboratory studies of tamoxifen and the related non-steroidal antioestrogen LY156,758 (keoxifene) undertaken as a prelude to initiating major trials in breast cancer prevention, described the pharmacology of SERMs that switch on and switch off target sites throughout the body. As an example of the immediate translation of the discovery of SERM action, tamoxifen was noted to block breast cancer growth but enhances the growth of endometrial cancer growth under laboratory conditions.[77] This laboratory concept translated to improved clinical care through awareness that tamoxifen increased the incidence of endometrial cancer in post-menopausal women treated for breast cancer. In another example of the application of SERMs, a failed breast cancer drug, keoxifene, was reinvented[42,72,78] as raloxifene, the first SERM to be successfully used to treat osteoporosis with the beneficial side-effect of preventing breast cancer indirectly.[79,80] Following rigorous testing in clinical trials,[81] raloxifene is now also available to prevent breast cancer in high risk post-menopausal women. The overall result of 30 years of translational research in breast cancer prevention is that there are now two therapeutic options, tamoxifen and raloxifene, for women who choose to reduce their risk of breast cancer.[81,82] Thirty years ago there were no choices. Based on clinical testing, tamoxifen has a good risk benefit ratio in pre-menopausal women[83] and raloxifene has a better safety profile in post-menopausal women.[81] It should be stressed, however, that raloxifene cannot be used to reduce breast cancer risk in premenopausal women.

Perhaps of greater significance is the fact that tamoxifen has become a pioneering agent to initiate new investigations in therapeutics. A study of the pharmacology of tamoxifen has been the catalyst to study the pharmacogenomics of tamoxifen which is redefining healthcare.[84] It appears that the specific metabolism of tamoxifen to a hydroxylated metabolite endoxifen is important for anticancer actions. This topic has recently been reviewed.[85] Finally, the importance of understanding the unique pharmacology of tamoxifen can be placed in perspective. In retrospect, tamoxifen could, in fact, be viewed as the lead compound that was essential to initiate the synthesis of a broad range of new SERMs for the treatment

of diseases as diverse as osteoporosis[86–92] and rheumatoid arthritis[93,94] and the subsequent extrapolation of the SERM concept to all members of the nuclear receptor superfamily.[76] The advances documented with targeting tamoxifen now offer the promise of designing drugs to treat diseases previously thought to be impossible.

Conflict of interest statement

None declared.

Acknowledgements

Dr. Jordan is supported by the Department of Defense Breast Program under Award Number BC050277 Center of Excellence (Views and opinions of, and endorsements by the author(s) do not reflect those of the US Army or the Department of Defense), FCCC Core Grant NIH P30 CA006927, R01-1620905, The Alfred G. Knudson Endowed Chair in Cancer Research and the Weg Fund of Fox Chase Cancer Center.

REFERENCES

1. Jordan VC, Koerner S. Tamoxifen (ICI 46,474) and the human carcinoma 8S oestrogen receptor. *Eur J Cancer* 1975;**11**:205–6.
2. Jordan VC. Effect of tamoxifen (ICI 46,474) on initiation and growth of DMBA-induced rat mammary carcinoma. *Eur J Cancer* 1976;**12**:419–24.
3. Jordan VC, Allen KE. Evaluation of the antitumour activity of the non-steroidal antioestrogen monohydroxytamoxifen in the DMBA-induced rat mammary carcinoma model. *Eur J Cancer* 1980;**16**:239–51.
4. Cooper RG. Combination chemotherapy in hormone resistant breast cancer. *Proc AACR* 1963;**10**:15.
5. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science* 1987;**235**:177–82.
6. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New Engl J Med* 2005;**353**:1673–84.
7. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *New Engl J Med* 2006;**354**:809–20.
8. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New Engl J Med* 2005;**353**:1659–72.
9. Jordan VC. Tamoxifen: a most unlikely pioneering medicine. *Nat Rev Drug Discov* 2003;**2**:205–13.
10. Jordan VC. The development of tamoxifen for breast cancer therapy: a tribute to the late Arthur L. Walpole. *Breast Cancer Res Treat* 1988;**11**(3):197–209.
11. Harper MJ, Walpole AL. Contrasting endocrine activities of cis and trans isomers in a series of substituted triphenylethylenes. *Nature* 1966;**212**(57):87.
12. Harper MJ, Walpole AL. A new derivative of triphenylethylene: effect on implantation and mode of action in rats. *J Reprod Fertil* 1967;**13**:101–19.
13. Cole MP, Jones CT, Todd ID. A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI 46474. *Br J Cancer* 1971;**25**:270–5.
14. Ward HW. Anti-oestrogen therapy for breast cancer: a trial of tamoxifen at two dose levels. *Br Med J* 1973;**1**(844):13–4.
15. Klopper A, Hall M. New synthetic agent for the induction of ovulation. Preliminary trial in women. *Br Med J* 1971;**1**:152–4.
16. Harper MJ, Walpole AL. Mode of action of I.C.I. 46,474 in preventing implantation in rats. *J Endocrinol* 1967;**37**(1):83–92.
17. Jordan VC. Tamoxifen (ICI 46,474) as a targeted therapy to treat and prevent breast cancer. *Brit J Pharmacol* 2006;**147**:S269–76.
18. Greenblatt RB, Roy S, Mahesh VB, Barfeld WE, Jungck EL. Induction of ovulation with clomiphene citrate. *Am J Obstet Gynecol* 1962;**84**:900–12.
19. Toft D, Gorski J. A receptor molecule for estrogens: isolation from the rat uterus and preliminary characterization. *Proc Natl Acad Sci USA* 1966;**55**(6):1574–81.
20. Toft D, Shyamala G, Gorski J. A receptor molecule for estrogens: studies using a cell-free system. *Proc Natl Acad Sci USA* 1967;**57**(6):1740–3.
21. Terenius L. Anti-oestrogens and breast cancer. *Eur J Cancer* 1971;**7**(1):57–64.
22. Lerner LJ, Holthaus JF, Thompson CR. A non-steroidal estrogen antagonist 1-(*p*-2-diethylaminoethoxyphenyl)-1-phenyl-2-*p*-methoxyphenylethanol. *Endocrinology* 1958;**63**:295–318.
23. Terenius L. Effect of anti-oestrogens on initiation of mammary cancer in the female rat. *Eur J Cancer* 1971;**7**:65–70.
24. Lerner LJ. The first non-steroidal antiestrogen-MER 25. In: Sutherland RL, Jordan VC, editors. *Nonsteroidal antioestrogens: molecular pharmacology and antitumour activity.* Sydney, Australia: Sydney Academic Press; 1981. p. 1–6.
25. Legha SS, Slavik M, Carter SK. Nafoxidine—an antiestrogen for the treatment of breast cancer. *Cancer* 1976;**38**(4):1535–41.
26. Nicholson RI, Golder MP. The effect of synthetic anti-oestrogens on the growth and biochemistry of rat mammary tumours. *Eur J Cancer* 1975;**11**(8):571–9.
27. Nicholson RI, Davies P, Griffiths K. Effects of oestradiol-17beta and tamoxifen on nuclear oestradiol-17beta receptors in DMBA-induced rat mammary tumours. *Eur J Cancer* 1977;**13**(3):201–8.
28. Nicholson RI, Golder MP, Davies P, Griffiths K. Effects of oestradiol-17beta and tamoxifen on total and accessible cytoplasmic oestradiol-17beta receptors in DMBA-induced rat mammary tumours. *Eur J Cancer* 1976;**12**(9):711–7.
29. Jordan VC, Koerner S. Tamoxifen as an anti-tumour agent: role of oestradiol and prolactin. *J Endocrinol* 1976;**68**(02):305–11.
30. Jordan VC, Jaspan T. Tamoxifen as an antitumour agent: oestrogen binding as a predictive test for tumour response. *J Endocrinol* 1976;**68**:453–60.
31. Jordan VC, Dowse LJ. Tamoxifen as an anti-tumour agent: effect on oestrogen binding. *J Endocrinol* 1976;**68**(02):297–303.
32. Jordan VC. Antiestrogenic and antitumor properties of tamoxifen in laboratory animals. *Cancer Treat Rep* 1976;**60**(10):1409–19.
33. Jordan VC, Dix CJ, Rowsby L, Prestwich G. Studies on the mechanism of action of the nonsteroidal antioestrogen tamoxifen (I.C.I. 46,474) in the rat. *Mol Cell Endocrinol* 1977;**7**(2):177–92.
34. Jordan VC, Prestwich G. Binding of [3H]tamoxifen in rat uterine cytosols: a comparison of swinging bucket and vertical tube rotor sucrose density gradient analysis. *Mol Cell Endocrinol* 1977;**8**(3):179–88.
35. Jordan VC, Collins MM, Rowsby L, Prestwich G. A monohydroxylated metabolite of tamoxifen with potent antioestrogenic activity. *J Endocrinol* 1977;**75**(2):305–16.
36. Allen KE, Clark ER, Jordan VC. Evidence for the metabolic activation of non-steroidal antioestrogens: a study of

structure–activity relationships. *Br J Pharmacol* 1980;**71**(1):83–91.
37. Shiau AK, Barstad D, Loria PM, et al. The structural basis of estrogen receptor/co-activator recognition and the antagonism of this interaction by tamoxifen. *Cell* 1998;**95**:927–37.
38. Lacassagne A. Hormonal pathogenesis of adenocarcinoma of the breast. *Am J Cancer* 1936;**27**:217–25.
39. Jordan VC. Antitumour activity of the antioestrogen ICI 46,474 (tamoxifen) in the dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model. *J Steroid Biochem* 1974;**5**:354.
40. Jordan VC, Allen KE, Dix CJ. Pharmacology of tamoxifen in laboratory animals. *Cancer Treat Rep* 1980;**64**(6-7):745–59.
41. Gottardis MM, Jordan VC. Antitumor actions of keoxifene and tamoxifen in the *N*-nitrosomethylurea-induced rat mammary carcinoma model. *Cancer Res* 1987;**47**(15):4020–4.
42. Jordan VC, Lababidi MK, Mirecki DM. Anti-oestrogenic and anti-tumour properties of prolonged tamoxifen therapy in C3H/OUJ mice. *Eur J Cancer* 1990;**26**(6):718–21.
43. Powles TJ, Hardy JR, Ashley SE, et al. A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* 1989;**60**(1):126–31.
44. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* 2007;**99**(4):283–90.
45. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;**90**:1371–88.
46. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet* 1998;**352**(9122):93–7.
47. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007;**99**(4):272–82.
48. Ingle JN, Ahmann DL, Green SJ, et al. Randomized clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer. *New Engl J Med* 1981;**304**:16–21.
49. Kiang DT, Kennedy BJ. Tamoxifen (antiestrogen) therapy in advanced breast cancer. *Ann Intern Med* 1977;**87**(6):687–90.
50. Fisher B, Carbone PP, Economou SG, et al. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. *New Engl J Med* 1975;**292**:117–22.
51. Bonadonna G, Bursamolino GE, Valaguss P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *New Engl J Med* 1976;**294**:405–10.
52. EBCTCG. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. *New Engl J Med* 1988;319(26):1681–92.
53. Jordan VC. The antioestrogen tamoxifen (ICI 46,474) as an antitumour agent. In: Proceedings of the eastern cooperative oncology group meeting, Miami, Florida; February 11–12, 1974.
54. Jordan VC. Tamoxifen mechanism of antitumour activity in animals and man. In: Proceedings of the eastern cooperative oncology group meeting, Jasper, Alberta; June 22–25, 1974.
55. Tamoxifen Workshop. In: Proceedings of the annual spring meeting of the primary breast cancer therapy group, Key Biscayne, Florida, April 28. *Cancer Treat Rep* 1976;60:1409–66.
56. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. Ludwig Breast Cancer Study Group. *Lancet* 1984;1(8389): 1256–60.
57. Pritchard KI, Meakin JW, Boyd NF, et al. A randomized trial of adjuvant tamoxifen in postmenopausal women with axillary node positive breast cancer. In: Jones SE, Salmon SE, editors. *Adjuvant therapy of breast cancer IV.* New York: Grune and Stratton; 1984. p. 339–48.
58. Rose C, Thorpe SM, Andersen KW, et al. Beneficial effect of adjuvant tamoxifen therapy in primary breast cancer patients with high oestrogen receptor values. *Lancet* 1985;**1**:16–29.
59. Ribeiro G, Palmer MK. Adjuvant tamoxifen for operable carcinoma of the breast: report of clinical trial by the Christie Hospital and Holt Radium Institute. *Br Med J (Clin Res Ed)* 1983;**286**(6368):827–30.
60. Ribeiro G, Swindell R. The Christie Hospital tamoxifen (Nolvadex) adjuvant trial for operable breast carcinoma—7-yr results. *Eur J Cancer Clin Oncol* 1985;**21**(8):897–900.
61. Lippman ME, Bolan G. Oestrogen-responsive human breast cancer in long term tissue culture. *Nature* 1975;**256**:592–3.
62. Huggins C, Grand LC, Brillantes FP. Mammary cancer induced by a single feeding of polynuclear hydrocarbons and their suppression. *Nature* 1961:189–204.
63. Jordan VC. Use of the DMBA-induced rat mammary carcinoma system for the evaluation of tamoxifen as a potential adjuvant therapy. *Rev Endocr-Relat Cancer* 1978(October Suppl.):49–55.
64. Jordan VC, Dix CJ, Allen KE. The effectiveness of long term tamoxifen treatment in a laboratory model for adjuvant hormone therapy of breast cancer. *Adjuvant Ther Cancer* 1979;**2**:19–26.
65. Goss PE, Ingle JN, Marino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New Engl J Med* 2003;**349**:1–10.
66. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;**97**:1262–71.
67. EBCTCG. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;354:1451–67.
68. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
69. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999;**353**(9169):1993–2000.
70. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003;**361**:296–300.
71. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;**97**:1652–62.
72. Jordan VC. Chemosuppression of breast cancer with tamoxifen: laboratory evidence and future clinical investigations. *Cancer Invest* 1988;**6**(5):589–95.
73. Lerner LJ, Jordan VC. The development of antiestrogens for the treatment of breast cancer: Eighth Cain Memorial Award Lecture. *Cancer Res* 1990;**50**:4177–89.
74. Jordan VC. Designer estrogens. *Sci Am* 1998;**279**(4):60–7.
75. Jordan VC. Selective estrogen receptor modulation: a personal perspective. *Cancer Res* 2001;**61**:5683–7.
76. Jordan VC, O'Malley BM. Selective estrogen receptor modulators and antihormonal resistance in breast cancer. *J Clin Oncol* 2007; in press, doi:10.1200/JCO.2007.11.3886.

77. Gottardis MM, Robinson SP, Satyaswaroop PG, Jordan VC. Contrasting actions of tamoxifen on endometrial and breast tumor growth in the athymic mouse. *Cancer Res* 1988;**48**:812–5.
78. Jordan VC, Phelps E, Lindgren JU. Effects of anti-estrogens on bone in castrated and intact female rats. *Breast Cancer Res Treat* 1987;**10**(1):31–5.
79. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999;**281**:2189–97.
80. Jordan VC. Optimising endocrine approaches for the chemoprevention of breast cancer. Beyond the Study of Tamoxifen and Raloxifene (STAR) trial. *Eur J Cancer* 2006;**42**:2909–13.
81. Vogel VG, Costantino JP, Wickerham DL, et al. The Study of Tamoxifen and Raloxifene (STAR): Report of the National Surgical Adjuvant Breast and Bowel Project P-2 Trial. *JAMA* 2006;**295**:2727–41.
82. Jordan VC. Tamoxifen or raloxifene for breast cancer chemoprevention: a tale of two choices. *Cancer Epidemiol Biomar Prev* 2007;**16**:2207–9.
83. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;**91**(21):1829–46.
84. Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005;**23**(36):9312–8.
85. Jordan VC. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. *Steroids* 2007;**72**:829–42.
86. Renaud J, Bischoff SF, Buhl T, et al. Estrogen receptor modulators: identification and structure–activity relationships of potent ERalpha-selective tetrahydroisoquinoline ligands. *J Med Chem* 2003;**46**:2945–57.
87. Kim S, Wu JY, Birzin ET, et al. Estrogen receptor ligands. II. Discovery of benzoxathiins as potent, selective estrogen receptor alpha modulators. *J Med Chem* 2004;**47**:2171–5.
88. Renaud J, Bischoff SF, Buhl T, et al. Selective estrogen receptor modulators with conformationally restricted side chains. Synthesis and structure–activity relationship of Eralpha-selective tetrahydroisoquinoline ligands. *J Med Chem* 2005;**48**:364–79.
89. Pigeon P, Top S, Vessieres A, et al. Selective estrogen receptor modulators in the ruthenocene series. Synthesis and biological behavior. *J Med Chem* 2005;**48**:2814–21.
90. Gungor T, Chen Y, Golla R, et al. Synthesis and characterization of 3-arylquinazolinone and 3-arylquinazolinethione derivatives as selective estrogen receptor beta modulators. *J Med Chem* 2006;**49**(8): 2440–55.
91. Jain N, Kanojia RM, Xu J, et al. Novel chromene-derived selective estrogen receptor modulators useful for alleviating hot flushes and vaginal dryness. *J Med Chem* 2006;**49**(11):3056–9.
92. Qin Z, Kastrati I, Chandrasena RE, et al. Benzothiophene selective estrogen receptor modulators with modulated oxidative activity and receptor affinity. *J Med Chem* 2007;**50**:2682–92.
93. Steffan RJ, Matelan E, Ashwell MA, et al. Synthesis and activity of substituted 4-(indazol-3-yl)phenols as pathway-selective estrogen receptor ligands useful in the treatment of rheumatoid arthritis. *J Med Chem* 2004;**47**(26):6435–8.
94. Keith Jr JC, Albert LM, Leathurby Y, et al. The utility of pathway selective estrogen receptor ligands that inhibit nuclear factor-kappa B transcriptional activity in models of rheumatoid arthritis. *Arthritis Res Ther* 2005;**7**(3):R427–38.
95. NATO. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer. Interim analysis at four years by Nolvadex Adjuvant Trial Organisation. *Lancet* 1983;1(8319):257–61.
96. Baum M, Brinkley DM, Dossett JA, et al. Improved survival among patients treated with adjuvant tamoxifen after mastectomy for early breast cancer [letter]. *Lancet* 1983;**2**(8347):450.
97. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet* 1987;2:171–5.
98. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. Swedish Breast Cancer Cooperative Group [see comments]. *J Natl Cancer Inst* 1996;88(21):1543–49.