

Preface

The story of tamoxifen is unique. This pioneering medicine was not conceived as part of a major development plan in the pharmaceutical industry to create a blockbuster, but rather tamoxifen (ICI46,474) was an orphan product that had failed its first indication as a “morning-after pill.” Breast cancer was a consideration, but the company terminated clinical development of the medicine in 1972. The resurrection of the medicine then occurred and, after a period of dismissal by the clinical community in the mid-1970s, successes went from strength to strength.

The success of the product depended upon individuals being in the right place at the right time and a “gentleman’s agreement” between industry (ICI Pharmaceuticals Division now AstraZeneca) and academia (Worcester Foundation and the Leeds University) to create a new strategy for the treatment and prevention of breast cancer. The gestation period for that strategy was the whole of the 1970s [1–4]. The principles conceived of targeting the tumor estrogen receptor (ER) and using long-term adjuvant endocrine therapy translated effectively to clinical trials that demonstrated dramatic and lasting reduction in mortality [5]. It is estimated that the hundreds of thousands, perhaps millions, of women are alive today because of the successful translation of research conducted in the 1970s.

Additionally, laboratory research on the prevention of mammary carcinogenesis [2, 3] in animals would translate to successful clinical trials [6–8] with tamoxifen being the first medicine to be approved by the Food and Drug Administration (FDA) for the reduction of the incidence of breast cancer in pre- and postmenopausal women at high risk. Tamoxifen was the first medicine to be approved to reduce the risk for any cancer.

Without the economic success of tamoxifen, there would have been no incentive to develop the aromatase inhibitors for the adjuvant treatment of ER-positive breast cancer in postmenopausal women. Without the study of the “good, the bad, and the ugly” of the tamoxifen, there would be no selective ER modulators (SERMs). The chance finding that tamoxifen and also a failed breast cancer drug keoxifene (to be renamed 5 or 6 years later as raloxifene) would maintain bone density in ovariectomized rats [9] opened the door to the suggestion that

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. [10]

Today, raloxifene is approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women and for the prevention of breast cancer in high-risk postmenopausal women [11]. However, tamoxifen became the pioneering SERM that switched on or switched off estrogen target sites around a woman's body. This new drug group also led to the idea of now being able to treat diseases via any member of the nuclear hormone receptor superfamily. Specificity would be enhanced and side effects reduced.

This monograph documents the milestones achieved during the curious twists and turns in the development of tamoxifen over the past 40 years. The story starts with the systemic synthesis of nonsteroidal estrogens that through serendipity suddenly gave us the nonsteroidal antiestrogens. The discovery by Leonard Lerner in the 1950s of MER25 (or ethamoxystriphenol) and subsequently clomiphene [10] and the finding that they were antifertility agents in rats [10] aroused the interest of the pharmaceutical industry to develop "morning-after pills." Nonsteroidal antiestrogens, however, were excellent contraceptives in rats but actually induced ovulation in subfertile women. Interest in nonsteroidal antiestrogens waned.

Cancer treatment was a consideration because of the known link between estrogen and the growth of some metastatic breast cancers. However, again there was no real enthusiasm from the pharmaceutical industry. Tamoxifen, after an unlikely start in the 1960s, advanced alone during the 1970s to become the "gold standard" for the antihormone treatment and prevention of breast cancer for the next 20 years. Despite all the "ups and downs" of the story, tamoxifen remains a cheap and effective lifesaving drug around the world. Indeed, the concept first described by our studies in the 1970s that "longer was better" as the treatment strategy for adjuvant therapy with tamoxifen for patients with ER-positive breast cancer continues to go from strength to strength in clinical trial. Ten years of adjuvant therapy is now known to be superior to 5 years of adjuvant therapy, but the profound decrease in mortality occurs during the decade after stopping tamoxifen at 10 years [12]. Again, there is a prediction we made in the 1990s that tamoxifen causes the evolution of drug resistance in the undetected micrometastases that exposes a vulnerability to estrogen-induced apoptosis in the tumor cells [13].

Lois Trench-Hanes generously accepted my invitation to contribute our Foreword. She was there at the beginning of tamoxifen in the United States and was the one who recruited me, on Arthur Walpole's recommendation, to advance the science and to support clinical development. We had many adventures over the years but her attitude of "get the job done" was essential to the start of this milestone. She was a force to be reckoned with, that through her willingness to see the project succeed for her company by establishing the correct clinical contacts not only propelled tamoxifen forward but helped my career development. She and

her husband George are lifelong friends and Lois is a godmother to my youngest daughter Alexandra (see pictures in Lois's Foreword).

This monograph has been put together by my Tamoxifen Team (VCJ) at the Lombardi Comprehensive Cancer Center at Georgetown University, Washington, DC. It is intended to illustrate and document the real journey traveled by this milestone in medicine.

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