Milestones in Drug Therapy
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Tamoxifen

Pioneering Medicine in Breast Cancer

Springer

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Thanks to all the "Tamoxifen Teams" who translated ideas into lives saved over the past 35 years

With the indispensable assistance of Fadeke Agboke, Puspanjali Bhatta, and Amy Botello

Foreword

I joined the Clinical Research Department of ICI Americas (ICI) in Wilmington, Delaware, in 1973, after competing in the World Championships for Rowing in Moscow, Russia, as a member of the first US women's rowing team. I mention this competition because as I was part of a team who was pioneering the international competition of women's crew, I was among the team at ICI who was pioneering the support and development of "targeted therapies," the first being tamoxifen. The operative word here is *team*. Having previously worked at the National Cancer Institute supporting the Breast Cancer Task Force, I was considered the most qualified individual at the time in the newly formed ICI to plan and organize the clinical investigation of the antiestrogen ICI46,474 in the United States!

I remember asking my director how long it takes to have a drug approved. He told me about 8 years; as a competitor, and not understanding all the aspects of pharmaceutical drug development, I said to myself, "We will do it *four years*." As it is known, the Food and Drug Administration (FDA) approved the labeling for tamoxifen on December 31, 1977, just 4 years and 5 months from the day I was hired. Thinking back over those early years, I recall a number of my colleagues as dedicated individuals who understood the importance of developing tamoxifen—Beverly Bach, Fran Ehrlich, David Sofi, and Bruce Decker—working in clinical research, regulatory affairs, market research, and marketing. Eventually, dozens of staff were all on the mission as a *team* to make tamoxifen available as quickly as possible to those patients who were most likely to benefit.

As you will read throughout this book, the early clinical development of tamoxifen was driven by clinical investigators and scientists in the United States, Canada, and Europe, who devoted their lives to the treatment of patients with breast cancer, such as Pierre Band, Harvey Lerner, and Lucien Israel. In fact, it was Harvey Lerner who demonstrated to Stuart Pharmaceuticals the urgency of continuing to develop this agent when the financial forecast was not compelling.

As you will read, the story of ICI46,474 began with its discovery in the fertility control program at ICI Pharmaceuticals, Alderley Park, Cheshire. It was an excellent morning-after pill in rats, but in fact stimulated ovulation in subfertile women. Although marketed in the United Kingdom for the induction of ovulation, the

agent's main focus in the United States was to treat breast cancer. A few small clinical studies of ICI46,474 conducted in Europe had reported modest activity in metastatic breast cancer (Cole et al. *British Journal of Cancer*, 1971;25:270–275 and Ward *British Medical Journal*, 1973;5844:13–14).

In the early 1970s, US clinical trial cooperative groups were focusing on the use of combination cytotoxic chemotherapy with the goal of curing breast cancer. Endocrine therapy was largely viewed as palliative; so there was little possibility that this antiestrogen would make much of an impact in the treatment of metastatic breast cancer or provide reasonable financial returns for investment in clinical studies. Then, in 1973, I met Craig Jordan, one of the few people in the world with a background in, and understanding of, the pharmacology of nonsteroidal antiestrogens. I arranged with my management to provide Craig with an unrestricted research grant at the Worcester Foundation and visited him to discuss the progress as he reinvented the strategic therapeutic use of ICI46,474 to become the drug tamoxifen that we know today. Craig's laboratory studies supported the exclusive use of tamoxifen to treat estrogen receptor (ER)-positive tumors. We used his results, prior to their publication, in our "investigators brochure."

I suggested that Craig become our scientific advisor for tamoxifen and arranged for him to meet the senior leadership of the Eastern Cooperative Oncology Group (ECOG): Doug Tormey, head of the ECOG Breast Committee, and Paul Carbone, chairman of ECOG. ICI Americas continued supporting his research, and in the laboratory, Craig discovered the strategy used today, that of long-term adjuvant tamoxifen therapy specifically targeting ER-positive breast tumors.

Looking at "the good, the bad, and the ugly" of tamoxifen, Craig's laboratory raised the question of whether the agent would increase the incidence of endometrial cancer. It did. This led to the recruitment of gynecologists to the breast cancer patient's care team, an extremely valuable advance at the end of the 1980s, as tamoxifen was about to be tested as a chemopreventive agent in high-risk women.

On a personal note, Craig and I had numerous adventures over the years, coincident with various clinical trial meetings. Here, I relate a story that demonstrates his philosophy of honoring commitment. In 1979, Craig was to be the opening speaker at the tamoxifen meeting in Sorrento, Italy. He was working in Bern, Switzerland, and was scheduled to fly down on an Alitalia flight from Zurich to Naples on the evening before his talk. Craig had to leave Zurich on the last flight that evening, as he had a site visit at the Ludwig Institute for Cancer Research in Bern earlier in the day. Then disaster struck. I learned that Alitalia was to go on strike that evening and urged him to leave Bern at lunch time, if there was to be any hope of his presenting at the meeting. Craig declared, "But I have a room full of site visitors from America—not possible," followed by, "Don't worry, I will be there." After my call, Craig immediately contacted his technician Brigitte Haldemann to drive him through the night over the 730 miles to Sorrento. With an hour to spare and after a shower, he presented his talk.

To this day, tamoxifen remains in the news. The Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial shows that 10 years of adjuvant tamoxifen is superior to 5 years of tamoxifen (Davies C et al., *Lancet*, 2012; epub 12/12/

2012). The therapeutic strategy is again being tested successfully, but the benefit in decreasing mortality occurs in the second decade after stopping longer-duration tamoxifen. This phenomenon (Wolf D, and Jordan VC, *Recent Results in Cancer Research*, 1993;127:23–33) led to the new biology of estrogen-induced apoptosis.

What happened to chemoprevention? Tamoxifen became the first agent to be approved by the Food and Drug Administration for reduction of breast cancer incidence in high-risk premenopausal and postmenopausal women. In January 2013, the National Institute for Health and Clinical Excellence (NICE) recommended tamoxifen be made available through the National Health Service in the United Kingdom for the chemoprevention of breast cancer.

This book tells the humanistic story of the development of tamoxifen. It is a tribute of gratitude to the tens of thousands of women and men who participated in clinical trials throughout the development of tamoxifen, which is now a therapeutic agent for the prevention as well as the treatment of minimal through advanced stages of breast cancer, depending on the patient's hormonal receptor status. It is also an acknowledgment of hundreds of clinical oncology health teams working to advance our understanding of the biology of breast cancer as well as thousands of clinicians caring for those with breast cancer.

I am amazed and so grateful that so many millions of lives have been extended and many more have benefited from the research and therapeutic strategies retold in this book. I am personally grateful to have played a role, minimal as it was and is, in the development of tamoxifen.

West Conshohocken, PA, USA

Lois Trench-Hines
Founder and Chief Executive Officer
Meniscus Limited

Pictured from *left* to *right*, George Hines, Lois Trench-Hines, Alexandra Jordan-Noel, and V. Craig Jordan. Photographed at a celebration at the Swiss Ambassador's Residence in Washington, DC, to celebrate the award of the St. Gallen Prize for Outstanding Accomplishments in the Adjuvant Treatment of Breast Cancer in 2011

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 ethamoxytriphetol) 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.

V. Craig Jordan
Russell E. McDaniel
Philipp Y. Maximov

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Acknowledgments

"We are in it for life"™
Tamoxifen Team Georgetown University

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Contents

About the Authors

V. Craig Jordan, OBE, Ph.D., D.Sc., FMedSci, member of the National Academy of Sciences, is known as the "father of tamoxifen." He was educated in England, obtaining his Ph.D. in Pharmacology (1973) studying a group of failed antifertility agents called nonsteroidal antiestrogens. There was no interest in drug development until then, but his work in academia blossomed into tamoxifen. Over a 40-year career, he researched all aspects of antiestrogens and then SERMs using structure-function relationships to investigate molecular mechanisms, developed new models, studied metabolism, developed the first realistic models of SERM resistance in vivo, and translated all of his concepts into clinical trials. He was there for the birth of tamoxifen as he is credited for reinventing a "failed morning-after contraceptive" to become the "gold standard" for the treatment of breast cancer. During his work, Jordan has held professorships at University of Wisconsin (1985–1993), Northwestern University (1993–2004) (also the Diana Princess of Wales Professor), the Fox Chase Cancer Center (2004–2009) (also the Alfred Knudson Professor), and currently Georgetown Lombardi Cancer Center where he is the scientific director. He has contributed more than 600 scientific articles with more than 23,000 citations. His work on SERMs has been recognized with the ACS Medal of Honor, the BMS Award, the Kettering Prize, the Karnofsky Award (ASCO), the Landon Award (AACR), and the St. Gallen Prize. He is a member of the National Academy of Sciences, Fellow of the Academy of Medical Sciences (UK), Fellow of the AACR Academy, one of the 90 honorary fellows of the Royal Society of Medicine worldwide, and he received the Order of the British Empire (OBE) for services to International Breast Cancer Research from Her Majesty Queen Elizabeth II in 2002. The chapters described in this book are all written by Dr. Jordan as he contributed personally to every aspect of tamoxifen application in