MCF-7: The First Hormone-responsive Breast Cancer Cell Line

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Introduction

On Thursday, January 2, 1997, Dr. Herbert Soule, the scientist who developed the MCF-7 breast cancer cell line, died. At the time, we were in the process of writing this tribute to mark the 25th anniversary of Dr. Soule’s remarkable accomplishment. The cells, derived from a breast cancer patient in the Detroit area and developed at the Michigan Cancer Foundation, Detroit, became a standard model in hundreds of laboratories around the world. In retrospect, the story of the diverse uses of these cells is really the history of our developing knowledge of hormone-regulated cell replication, and they provided a unique insight into the endocrine therapy of breast cancer.

Our article is offered as a tribute and memorial to Dr. Soule. We will trace research with MCF-7 cells to illustrate the change in our ideas about cell replication and to highlight the advances in our understanding of the signal transduction pathway of estrogen and the molecular biology of estrogen action. All of these advances depended on the unique properties of MCF-7 cells. Additionally, it is important to appreciate that the cell system has now found applications in experimental therapeutics, and the results from these studies are being translated to the clinic for the treatment of patients. None of this would have been possible without Dr. Soule’s skill as a cell biologist.

Characterization

The MCF-7 breast cancer cell line was derived from a pleural effusion taken from a patient with metastatic breast cancer (1). The 69-year-old patient had undergone a mastectomy of her right breast for a benign tumor and a radical mastectomy of her left breast for a malignant adenocarcinoma 7 and 3 years, respectively, before primary culture of cells was started. Interestingly, the Soule et al. article (1) notes that local recurrences were controlled for 3 years with radiotherapy and hormone therapy. In the days before tamoxifen, the patient was probably treated with high doses of the synthetic estrogen diethylstilbestrol. Clearly, the disease was very hormone responsive, because it was controlled for three times longer than the 1-year average to be expected. Two months after widespread nodular recurrences occurred, in June of 1970, samples were taken from a pleural effusion for laboratory studies. The cells were proven to be of human origin, and cytogenetic studies indicated a distinct stem line of 88 chromosomes. Dr. Sam Brooks, working with Dr. Soule (2), first described the ER3 in MCF-7 cells by both Scatchard and sucrose density gradient analysis. This was a pivotal discovery.

From this point onward, research accelerated rapidly. In 1975, Dr. Marc Lippman (3) demonstrated that the antiestrogen tamoxifen inhibited the growth of MCF-7 cells, but the inhibition could be reversed by estrogen. The drug was classified as a competitive inhibitor of estrogen action, but at high concentrations tamoxifen killed cells. Because these results appeared to parallel the emerging clinical observations (4), Lippman (3) went on to predict a future path for endocrine research: “The potential value of a hormone-dependent human breast cancer in long term tissue culture for the study of mechanism(s) by which steroid hormones exert their trophic effects is significant, particularly in view of the likelihood of obtaining regulatory variants or mutants which are hormone independent.” At about the same time, Kathryn Horwitz, who was completing her Ph.D. in the late Dr. Bill McGuire’s laboratory, identified the receptors for glucocorticoids, progestins, and androgens, as well as the ER (5). She concluded, “MCF-7 may be an excellent in vitro model for studying the mechanism of tumor response to endocrine therapy as well as the complex relationships between binding and biological actions of these hormones” (5). The predictions from both research programs were to be proved correct over the next 2 decades.

Horwitz and McGuire focused initially on the regulation of PgR synthesis in MCF-7 cells by estrogens and antiestrogens. They developed a large body of evidence to associate processing (destruction) of nuclear receptor complexes with the initiation of PgR synthesis (6, 7). This work paralleled their suggestion of using PgR assays as a predictive test for hormone-dependent breast cancer (8). Turning to the effects of antiestrogens, Horwitz et al. (9) found that tamoxifen is sufficiently estrogenic to initiate PgR synthesis by itself. The estrogenic properties of tamoxifen would subsequently be important to explain the additional benefits of tamoxifen on bones and lipids and the possible development of drug resistance (10). However, at that time in the late 1970s, work on the antiproliferative actions of antiestrogens was of paramount importance. Tamoxifen and other compounds were shown to inhibit replication (11). Drs. Rob Sutherland (12, 13) and Kent Osborne (14, 15) would demonstrate subsequently, using MCF-7 cells, that tamoxifen produces a reversible block in the G1 phase of the cell cycle.

Despite the interesting findings with antiestrogens, the central focus of laboratory research in the 1970s and early 1980s was to prove that estrogen actually stimulated tumor growth directly. Dogma predicted that the MCF-7 ER-positive cell line should grow faster with exogenous estrogen. The experiment could be accomplished routinely if cells first were treated with antiestrogens for a few days. Estrogen could “rescue” antiestrogen-blocked cells (3), but the effects of estrogen alone were less dramatic. Here was a paradox.

Cells Grown in Estrogen

Although Lippman’s group consistently demonstrated stimulatory effects with estrogen using [3H]thymidine incorporation as a method of monitoring DNA replication (3, 11, 16), others were unable to show profound effects on cell proliferation (17–19). This led to intense debate (20) and also to the suggestion that estrogen really produced...
growth by an indirect method (21). This latter conclusion was based on the observation that estrogen did not stimulate MCF-7 cells to replicate in vitro, but if the same cells were grown in athymic mice, then estrogen stimulated growth. It was reasoned that estrogen must be triggering a second messenger in vivo. At the time (1980), this was not an unreasonable conclusion, because it was accepted that carcinogen-induced rat mammary tumors require both estrogen and estrogen-stimulated prolactin for growth (22). Subsequently, Huseby et al. (23), at the Michigan Cancer Foundation, provided evidence, in athymic mice, to demonstrate that estrogen had a direct growth-stimulating effect on MCF-7 tumor cells in vivo. Indirect growth stimulation through a second messenger was improbable.

The breakthrough in our understanding of direct estrogen action came with the discovery that MCF-7 cells had been grown in estrogen-containing media from the start. Indeed, if the occult estrogen had not been there, the MCF-7 cell model would not have been possible.

The story unfolded through a series of fortuitous accidents. Dr. John Katzenellenbogen was particularly interested in developing a fluorescent-tagged estrogen so that ER could be detected easily in breast cancer specimens under the fluorescence microscope. Naturally, he was using MCF-7 cells as his laboratory model, but the finding that unwashed cells fluoresced led to an examination of the chemical constituents in media. Phenol red (Fig. 1) is the indicator used routinely in commercial media to monitor the oxidative state of the cells. The indicator is, however, present not as a few drops but in µM concentrations, and its structure is reminiscent of nonsteroidal estrogens first synthesized by Sir Charles Dodds in the 1930s (24) prior to his landmark discovery of diethylstilbestrol (25). Drs. John and Benita Katzenellenbogen established, in a seminal publication, that removal of phenol red from media resulted in the exquisite sensitivity of MCF-7 cells to the growth-promoting effects of estrogen (26). As predicted from data, in vivo antiestrogens were partial agonists and were antagonists of estradiol action.

As an aside, it was found that different preparations of phenol red had different potencies as estrogens (27), and it was a dimerization product, which occurred during manufacture, that was responsible for estrogenicity (28, 29). The similarity of the structure of the contaminant with the most potent synthetic estrogen, diethylstilbestrol, is illustrated in Fig. 1.

The discovery of an occult estrogen that is ubiquitously present in the culture media is an important lesson, obvious in hindsight, but pivotal to all of the subsequent progress in the understanding and interpretation of data obtained with MCF-7 cells in culture.

Monoclonal Antibodies to the ER

The discovery and detection of the ER protein (30–33) in the rat uterus was of fundamental importance to progress in breast cancer therapy. However, studies on the biochemistry of the protein involved expensive experiments using rats or the collection of calf uteri from slaughterhouses. Clearly, the development of antibodies to the human receptor would be extremely important in research and for the convenient detection of ER by clinical laboratories.

Progress in the detection of the ER using antibodies primarily centered on Jensen’s group at the Ben May Laboratory in Chicago. Polyclonal antibodies against ER protein were obtained initially using highly purified ER as an antigen to immunize rabbits and a goat (34, 35). To avoid the heterogeneity in the antibodies, the hybridoma techniques of Kohler and Milstein (36) were used subsequently to obtain monoclonal antibodies to the calf uterine nuclear ER (37). Unfortunately, there was no absolute proof that monoclonal antibodies to animal ER would be of value for human studies. Almost immediately, but working in collaboration with scientists at Abbott Laboratories, Dr. Geo Greene, who played the leading experimental role in the antibody research at the Ben May Laboratories, described the preparation of monoclonal antibodies to the human ER from MCF-7 breast cancer cells (38). The property of the cells to replicate indefinitely under carefully controlled conditions provided a constant supply of receptor to make antibodies.

Although the development of monoclonal antibodies to the ER would ultimately revolutionize the detection of ER in clinical breast cancer samples, the new laboratory tool would also change the subcellular model of estrogen action. The original model for estrogen action placed the ER in the cytoplasmic compartment. Estrogen bound to the receptor and caused translocation of the complex to the nucleus, where the events associated with hormone action would be triggered. This model had been challenged in 1977 by Zava and McGuire, who used careful fractionation methods and found unoccupied ER in the nuclear compartment of MCF-7 cells (39). However, the ability to see receptor without cell disruption would change the textbook model that had stood for nearly 2 decades.

King and Greene (40) used monoclonal antibodies to the MCF-7 ER to demonstrate that ER was in the nucleus of cells. Although the results were published before the discovery that MCF-7 cells were actually growing in the estrogenic phenol red-containing media, these data (Fig. 2) altered the scientific concepts. Parallel studies by Welshons et al. (41), who used cytochalasin B to prepare nucleoplasts from the rat pituitary cell line GH3, found that the majority of ER was contained in the nucleoplasm and not the cytoplasm. Subsequently, Welshons et al. (42) showed that nucleoplasm from MCF-7 cells grown in phenol red-free media contained ER. Thus, it would not be unreasonable to state that the MCF-7 cell line was essential for the understanding of the subcellular organization of not only the ER but also all of the other steroid hormone systems. The importance of the development of monoclonal antibodies to ER extends to mechanistic studies of receptor dynamics during estrogen and antiestrogen action (43, 44). Additionally, antibodies can be used as probes to study the direct effects of antiestrogens on the ER protein (45, 46). Indeed, an additional epitope has been discovered to occur when ER is liganded with 4-hydroxytamoxifen (47), and this may be important to understand antiestrogen action.

![Fig. 1. Structures of estrogenic components identified in tissue culture media and the most potent synthetic nonsteroidal estrogen, diethylstilbestrol.](image-url)
Cloning and Sequencing of the ER

Without the preparation of monoclonal antibodies to the MCF-7 ER, it would not have been possible to make progress in cloning and sequencing the ER from MCF-7 cells (48). The development of probes that hybridized in the cDNA library prepared from MCF-7 cells resulted in two simultaneous reports of the sequencing and expression of the full-length cDNA for ER (49, 50). However, it was noted initially that there was an alteration in the cloned MCF-7 ER cDNA [Gly-400 (GGG) \( \rightarrow \) Val-400 (GTG)]. Other species (chicken, mouse, rat, and Xenopus) all have a glycine at position 400, but initial speculation discounted the relevance of the finding for the human ER, because the binding affinity for estradiol was unaffected at 4°C (50, 51). However, it was concluded eventually that the original cDNA designated HEO produced a protein that has decreased affinity for estradiol at 25°C (52), and it is, because of the mutation, unstable and rapidly turned over when expressed in cells. Subsequently, it was also found that the mutation increases the estrogen-like activity of tamoxifen (53, 54). The wild-type ER from MCF-7 cells is now referred to as HEGO, with G denoting the presence of glycine at position 400.

The human ER gene is >140 kb in length and is split into eight exons with the position of the introns highly conserved with other receptors (51). The MCF-7 ER mRNA is 6322 nucleotides in length and encodes a 595-amino acid protein (50). The functional organization of the ER has been demonstrated by site-directed mutagenesis (55). The human ER comprises six regions (regions A–F), with a small, centrally located DNA-binding domain and a large, COOH-terminal ligand-binding domain (Fig. 3). The development of reverse transcription-PCR (56) allowed a close examination of the mRNAs from MCF-7 cells to establish whether variants of the ER exist and whether these could have biological relevance. The research strategy is controversial, because there is only clear evidence that the variants actually produce a protein in one subline of MCF-7 cells called 2A (57). The protein is a high molecular weight ER variant \( (M_r, 77,000 \ \text{rather \ than \ } M_r, 65,000) \) that does not bind estradiol or antiestrogens (58). This is because the protein has a duplication of exons 6 and 7 in the ligand-binding domain (58, 59). Other investigators using reverse transcription-PCR have produced variant cDNA from MCF-7 cells (60); however, the biological relevance of any of the variants has recently been questioned (61–63).

Growth Factor Regulation

The MCF-7 cell model has been examined extensively to determine the mechanism(s) of estrogen-stimulated growth. The early work of Dr. Henri Rochefort identified a secreted glycoprotein from MCF-7 cells that was believed originally to be a growth accelerator (64, 65). However, identification of the protein with monoclonal antibodies (66) and the cloning and sequencing of the gene showed the protein to be the enzyme cathepsin D (67). The clinical community has extensively studied the protein as a potential marker of prognosis in node-positive and node-negative breast cancer. In contrast, a protein of unknown function, pS2, was identified in MCF-7 cells by Chambon's group (68–70). The protein has, like the PgR, been linked to good prognosis in breast cancer. The estrogen response element for pS2 is used routinely as an analytical system for reporter genes to study the molecular biology of ER activation (e.g., see Ref. 71).

The major conceptual breakthrough in our understanding of cellular communication occurred in the late 1970s with the identification of positive and negative growth factors. It was reasoned that a link must exist between estrogen action and growth factor secretion. Lippman's group used MCF-7 cells extensively throughout the 1980s to describe the hormonal regulation of the TGF-\( \alpha \)/epidermal growth factor receptor system (72–76). This has been particularly difficult to accomplish, because, unlike hormone-independent cells that overexpress growth factors and their receptors, the MCF-7 system has only low levels of the relevant components. Studies showed initially that factors secreted...
from MCF-7 cells could support the growth of the same cells in athymic mice (77); however, the transfection of TGF-α cDNA into MCF-7 was not, by itself, able to provoke estrogen-independent growth in animals (78). Nevertheless, transfection of v-rasH does cause an elevation of stimulatory growth factors that can support cell growth in animals (79, 80) and the interaction of MCF-7 cells with basement membranes (81). Lippman’s group also described antiestrogen-induced production of the inhibitory growth factor TGF-β (82). In fact, these studies were performed before the knowledge that MCF-7 cells were grown in phenol red and the realization that the estrogenic contaminant was blocking TGF-β synthesis. Despite this, the principle was clear. Antiestrogens could maintain the secretion of TGF-β from ER-positive cells, and the growth factor could have a paracrine role in inhibiting the growth of adjacent ER-negative cells (82).

The MCF-7 cells provided an experimental system for defining the role of insulin and IGFs in the estrogen-induced proliferation of breast cancer cells. Although IGF-I and IGF-II mRNAs are detected easily in the majority of breast tumors, conflicting results have been reported for the expression of IGFs in breast cancer cells. Initially, Huff et al. (83, 84) reported that IGF-I is synthesized under estrogen control in MCF-7 cells. However, Karey and Sirbasku (85), using an immunoassay to measure IGF-I in conditioned medium, reported that MCF-7 cells do not produce biologically significant concentrations of IGF-I, and subsequently, Yee et al. (86), using a sensitive RNase protection assay, could not detect IGF-I mRNA in breast cancer cell lines, including MCF-7 cells.

The major mitogenic effects of both IGF-I and IGF-II are thought to be mediated via the type I IGF receptor identified in MCF-7 cells as well as in other breast cancer cells (87-89). The action of IGF-I at its receptor may be modified by IGF-binding proteins, which have been identified in conditioned media from breast cancer cells, including MCF-7 cells (90, 91). It has been shown that tamoxifen resistance and estrogen independence in human breast cancer cells is associated with complex changes in IGF-binding protein secretion patterns that accompany changes in IGF receptor expression (92).

Despite the appeal of the autocrine model of growth regulation in breast cancer by different growth factors, the data are not consistent with an autocrine model of estrogen-regulated growth involving IGF-I and IGF-II. In the nude mouse model, antibody-induced blockade of the type I IGF receptor does not affect growth of the MCF-7 tumors, whereas the antibody inhibits growth of estrogen-independent MDA-MB-231 tumors (93). However, a stimulatory effect of exogenous IGF-I on MCF-7 tumor growth in nude mice has been reported (94), suggesting that these cells do not lose the type I IGF receptors in vivo. Experiments in vitro with phenol red-free medium demonstrate that IGF-I alone has very little effect on cell proliferation and only in the presence of estradiol can these agents act synergistically to stimulate growth (95-97). The observation that estradiol regulates type I IGF receptor in MCF-7 cells at the transcriptional level (95) suggests a direct sensitization of breast cancer cells to IGFs by estradiol.

Hormone and Antiestrogen Resistance in Vitro

It has been a century since the first observation that some human breast cancers will regress if estrogen is withdrawn (98). Naturally, the development of antiestrogens as a successful breast cancer therapy (99) resulted in the quest to understand antiestrogen resistance and the link to hormone-independent growth. In the laboratories, MCF-7 cells were used to develop several antiestrogen-resistant cell lines (100), one of which, LYT2 (101), was found subsequently to have a wild-type ER (102). The finding of wild-type receptors is a consistent finding in antiestrogen-resistant disease. Early laboratory studies to develop antiestrogen-resistant breast cancer cell growth were successful because the antiestrogen completely saturated receptors. In contrast, a study of the direct effects of estrogen withdrawal on hormone-responsive breast cancer cells was not possible until the discovery of phenol red in the media (26).

The first two published reports of the effects of phenol red-free media on the growth of MCF-7 cells came to the same conclusions (103, 104). The cells increase their growth rate as adapted clones grow out. There is an increase in the levels of ER, but PgR synthesis ceases. Estrogen can reinduce the PgR; however, there is little effect on cell growth rate. The cells now appear to grow maximally in the absence of ligand but remain sensitive to the inhibitory actions of antiestrogen. In fact, Masamura et al. (105) have demonstrated subsequently that estrogen-deprived MCF-7 cells become hypersensitive to estradiol.

Several cell lines have subsequently been cloned from the surviving MCF-7 cells in an estrogen-free medium. The line MCF-7.5C is ER positive (wild type), but PgR cannot be induced by estrogen (106). If the original MCF-7 could be described as making up the ER-positive PgR-positive tumor that has a functioning receptor with good prognosis, then the MCF-7.5C cells make up the ER-positive PgR-negative tumor that has a poorer prognosis (107). Dr. Benita Katzenellenbogen has also developed numerous new cell lines from MCF-7 (108), and their growth characteristics have been described in athymic animals by Dr. Robert Clark at Georgetown University in Washington, D.C. (109). Additionally, Dr. Katzenellenbogen has recently described a tamoxifen (resistant)-stimulated breast cancer cell line derived from MCF-7 cells in vitro (110). The cells are extremely valuable to compare and contrast with wild-type lines by differential display. Identification and elucidation of the new growth pathways in the tamoxifen-resistant ER-positive cells will have important implications for the design of new therapeutic agents.

Tamoxifen-stimulated Tumor Growth

The development of immunodeficient athymic mice (111) provided a new dimension for the study of breast cancer growth in vivo. Regrettably, early studies with primary breast tumors were, in the main, unsuccessful in producing hormone-responsive disease, because tumor takes were poor, and hormone-independent disease usually grew preferentially despite estrogen administration (112-114).

The breakthrough came with the transplantation of the breast cancer cell line MCF-7 (115). Estrogen is required for the growth of MCF-7 breast cancer cells in ovariectomized athymic mice. It should be noted, however, that MCF-7 cells do not grow vigorously in intact athymic mice, because the animals have endocrine deficiencies and do not have estrous cycles. Estrogen supplementation is obligatory (116). However, there are considerable variations in MCF-7 cell lines, and this produces different abilities to grow in athymic mice (117).

It is interesting to note that, although tamoxifen is described as estrogen in the mouse (118), tamoxifen does not initially support the growth of MCF-7 cells. Tamoxifen inhibits estrogen-stimulated MCF-7 tumor growth in vivo (119, 120). This observation parallels the observations in vitro. Tamoxifen does, however, maintain occult disease for long periods after inoculation into mice, and tumors can be reactivated by estrogen treatment when the drug is stopped (120).

By the mid-1980s, prolonged (2-5 years) adjuvant tamoxifen treatment was being used routinely in clinical practice, and it was clear that this strategy produced a survival advantage (121, 122). However, it was unreasonable to expect that drug resistance would not occur eventually. An endometrial carcinoma, EnCa101, had been shown to grow partially during tamoxifen treatment (123), so it was possible that tamoxifen-stimulated breast cancer would also occur. Osborne et al. (124) first showed that MCF-7 cells could become tamoxifen...
stimulated for growth in vivo but, paradoxically, in vitro, the tumor cells revert to their original phenotype; i.e., tamoxifen blocks estrogen-stimulated growth. In parallel studies, we showed (125) that tamoxifen-stimulated breast tumors grown from MCF-7 cells could be passaged routinely and the tumors would grow in vivo in response to either estradiol or tamoxifen. Furthermore, tamoxifen-stimulated tumors grow in athymic rats and natural killer cell-deficient (beige) mice (126), so the growth effect is neither species nor immunology specific. In fact, target site-specific actions of tamoxifen were noted in the animals. The uteri in mice treated with tamoxifen become quiescent and refractory to estrogen, despite the fact that a tamoxifen-stimulated breast tumor is growing in the host (125).

The model of tamoxifen resistance in breast cancer appears to be unique to MCF-7 cells, and there is intense interest in discovering the mechanism of tamoxifen-stimulated tumor growth. Early theories that the receptor may be mutated have proved to be incorrect. Despite one exception, with a 351ala→ tyr mutant ER (127) that is observed in one transplant line, the majority of tumors have wild-type ER (128). Similarly, ideas that tamoxifen might be metabolized peripherally to estrogens (129, 130) or locally (131—133) in the MCF-7 tumor have not been supported by experimentation. The growth (134) and development of tamoxifen-stimulated MCF-7 tumors (135) occurs with analogues that are incapable of being converted to estrogenic metabolites. Clearly, the cells are using the intrinsic efficacy of the antiestrogen-ER complex to drive cell replication by an alternate pathway.

Most importantly, compounds such as ICI 164,384 and ICI 182,780 (pure antiestrogens), which have no intrinsic estrogenic properties in estrogen target tissues (136), inhibit the growth of tamoxifen-stimulated MCF-7 tumors in vivo (137, 138).

Clinical Advances and the Future Possibilities

It would be inappropriate to finish this story of the laboratory discoveries made possible by MCF-7 cells without a brief mention of some of the clinical advances that have occurred. The systematic dissection of hormone action has led to significant progress in the treatment of breast cancer. The following list of examples is itself impressive but does not claim to be exhaustive.

Abbott Laboratories developed kits for the quantitation of ER (ER-EIA) and PgR (PgR-EIA) in breast tumor (139—141). Steroid receptors from MCF-7 cells were key to this innovation. Specific monoclonal antibodies for ER and PgR are now used routinely to determine receptors in tumor cells by flow cytometry and to determine the heterogeneity of cell populations in small biopsy samples (142—144).

The ubiquitous use of long-term adjuvant tamoxifen therapy (145) originally presented a problem for the determination of receptor status of recurrences using conventional ligand-binding assays. Tamoxifen and metabolites saturate all of the tissues and produce false-negative results in breast cancer biopsies because of receptor occupancy. Monoclonal antibodies changed all of that, and it is now known that many recurrences remain receptor positive (146). Additionally, there is evidence that tamoxifen-stimulated disease occurs in patients (147), which is analogous to the tamoxifen-stimulated MCF-7 tumor in the laboratories that remains receptor positive (128).

The ability of pure antiestrogens to control the growth of tamoxifen-stimulated MCF-7 tumors (137, 138) was strong evidence to progress toward clinical trials. Currently, ICI 182,780, the first of several pure antiestrogens, is being performed as predicted. Preliminary trials (148) indicate good patient acceptability, a response rate of about 30%, and a duration of response that extends for several years. During the past 25 years, the symbiotic relationship between laboratory research and clinical investigations has resulted in clear advances in our knowledge of hormone action and the standardization of therapy with antiestrogenic drugs. Dr. Herbert Soule had the vision and good fortune to establish the first hormone-responsive breast cancer cell line that played a fundamental role in advancing knowledge. He was involved in the three key studies: cell characterization (1), receptor identification (2), and estrogen-stimulated growth in athymic mice (115). Together, the results of his labs revolutionized the opportunities for breast cancer research. In retrospect, it is remarkable that this single cell line has contributed so much to our basic understanding of hormone action and the treatment possibilities in breast cancer. However, the story does not end here. Dr. Soule left a second legacy, MCF-10 (149, 150).

The research challenge for the 21st century is to prevent breast cancer. MCF-10 and its variant cells are, surprisingly, naturally immortalized, normal epithelial cells of mammary origin that do not produce tumors in athymic animals (151). The key for a future generation of research workers is to dissect the molecular events involved in the change from normal to malignant breast epithelium (152—155). It is our belief that by diligent research endeavors, and the example of MCF-7 cells before, the MCF-10 cells can be used effectively to formulate a rational strategy for the prevention of breast cancer.

Acknowledgments

This history is offered as a tribute and memorial to Dr. Herbert Soule and the staff of the Michigan Cancer Foundation, who made possible the development of the remarkable MCF-7 breast cancer cell line. It is also dedicated to Sister Catherine Frances, the patient with breast cancer whose cells ultimately extended the lives of thousands of women. We offer this history as a prime example of the value of laboratory research that translates, over decades, to the aid of patients with breast cancer.

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