Bernard Fisher has recently stated, “A clinical trial is just a mechanism by which to evaluate what you have done in the laboratory” (Oncology News International, March 2008). In this issue of the Journal, Grady et al. (1) have analyzed the incidence of invasive breast cancer in a clinical trial of women treated with raloxifene with the intention of reducing their risk of dying from coronary heart disease. To the casual observer, an analysis of this nature would seem to be unusual, if not a bit bizarre, but the fact is that raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen-like activity to reduce low-density lipid (LDL) cholesterol (2) and to reduce the risk of fractures in osteoporosis (3), and antiestrogenic properties to block the growth of breast cancers (4). When the Raloxifene Use for the Heart (RUTH) trial started, raloxifene was approved for the prevention of osteoporosis in high-risk postmenopausal women, and it was known from clinical trials that raloxifene produced a decrease in invasive breast cancer (5). So where did all the ideas come from to examine these qualities of raloxifene, which had previously failed its original application as a breast cancer drug (6)? The answer is the laboratory.

Raloxifene started life in the laboratories at Eli Lilly as Y156758, a nonsteroidal antiestrogen (7) with a high affinity for the estrogen receptor (ER) (8) and a primary application as a treatment for breast cancer. Regrettably, this polyhydroxylated class of drugs has a very short biological half-life (9) and subsequent clinical studies with the drug under the name keoxifene also showed virtually no activity in patients who had failed tamoxifen treatment (10). Further development as a breast cancer therapy was abandoned in the late 1980s. However, at this time, selective ER modulation was recognized (11–13) for “nonsteroidal antiestrogens” (tamoxifen and raloxifene are members of this class) and a new opportunity occurred for clinical development (14). This opportunity was based on the laboratory finding that tamoxifen and keoxifene (aka raloxifene) simultaneously maintained bone density in ovariectomized rats (12) and inhibited rat mammary carcinogenesis (15). These findings rapidly translated into the hypothesis that perhaps one could reduce the risk of breast cancer by treating women with a drug that maintained bone density, thereby reducing the risk of osteoporosis. It was well known that this class of drugs lowered circulating cholesterol in laboratory

The Rise of Raloxifene and the Fall of Invasive Breast Cancer

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animals; in fact, tamoxifen had a patent as a potential hypocholesteremic agent since the 1960s (16,17). Based on all of these laboratory data, a clinical development strategy was simply stated that was to eventually resurface and catalyze the rise of raloxifene (18):

Nevertheless there is a real concern about being able to target the right population [for prevention]. We cannot predict who will develop breast cancer; we can only guess at the probability. Furthermore “high risk” women are, in fact, only a minority of those who will develop breast cancer so any success must be balanced against as yet unknown accumulative toxicities. Is this the end of the possible applications for antiestrogens? Certainly not. We have obtained valuable clinical information about this group of drugs that can be used in other disease states. Research does not travel in straight lines and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous application of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be postmenopausal women in general, thereby avoiding the requirement to select a high risk group to prevent breast cancer.

In the late 1980s and early 1990s, clinical studies were exploring the pharmacology of tamoxifen as a prelude to its use in high-risk women as a potential chemopreventive agent. What was found was that tamoxifen lowered LDL cholesterol in postmenopausal women but did not affect high-density lipid cholesterol (19,20). More importantly, tamoxifen enhanced spinal bone density compared with placebo in a randomized clinical study of postmenopausal women (21). It was about this time that scientists at Eli Lilly confirmed (22) the findings of the earlier laboratory studies that raloxifene had potential for maintaining bone density (12) and also lowered circulating cholesterol. The scene was therefore set to test raloxifene as a SERM to prevent fractures from osteoporosis in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (1994) and, subsequently, to initiate the RUTH trial (1998). Both trials naturally evaluated the original hypothesis that multiple diseases could potentially be controlled with a SERM, thereby enhancing public health (14,18). It is now clear based on clinical trials data, however, that raloxifene is not effective to reduce the risk of coronary heart disease (23,24). It could be that patients recruited to the RUTH trial have disease that is too far advanced for the modest reductions in LDL cholesterol to have any impact on pathology. The SERM approach may work only in patients who have very early atherosclerotic lesions so that long-term therapy can effectively retard the development of pathology. In the years to come, it may be impossible to answer this question by examining populations of women who are using raloxifene to prevent osteoporosis because of the widespread use of statins to reduce LDL cholesterol.

One interesting aspect of the study of Grady et al. (1) is the 44% reduction in invasive breast cancer, which also comprises a 55% reduction in invasive ER-positive breast cancer. This placebo-controlled study can be compared with the Study of Tamoxifen and Raloxifene (STAR), where raloxifene was noted to be equivalent to tamoxifen at reducing the risk of breast cancer (25). Although the STAR, was not placebo controlled, in Fisher’s pioneering placebo-controlled tamoxifen study, the National Surgical Adjuvant Breast and Bowel Project P-1 trial, there was a 50% reduction in invasive breast cancer and a 69% reduction in ER-positive breast cancer (26,27). Overall, these data contrast with the MORE trial, in which there was a 76% decrease in invasive breast cancer and 90% decrease in ER-positive breast cancer. The question is why? One plausible explanation for the greater reduction in invasive breast cancer in the MORE trial than in the RUTH and STAR trials could be the low circulating levels of estradiol in postmenopausal women at risk for osteoporosis compared with those in women in both the RUTH and STAR trials. The polyphenolic compounds related to raloxifene are competitive inhibitors of estrogen action, and it is also known that raloxifene has only a 2% bioavailability, with rapid excretion (28). Once patients become noncompliant about taking raloxifene, there would be no protection for the development of invasive breast cancer. Although the numbers are very small in the study of Grady et al. (1) and the MORE trial (5), raloxifene appears to be poor at controlling the risk of developing noninvasive carcinomas. Indeed, tamoxifen seems to be marginally superior to raloxifene in controlling noninvasive breast cancer in the STAR trial (25).

Overall, clinical evidence is accumulating that the SERMs hold great promise in being able to control multiple diseases (29). This is the good news because, until recently, it was generally believed that hormone replacement therapy was the answer to controlling the development of coronary heart disease and osteoporosis, but at the price of an enhanced risk of invasive breast cancer (30,31). For the future, this is no longer acceptable and the SERMs may be one way of further advancing targeted public health.

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