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COMMENTARY

Beyond raloxifene for the prevention of osteoporosis and breast cancer

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Selective oestrogen receptor modulators (SERMs) can build bone in the postmenopausal woman and lower circulating cholesterol. These oestrogen-like properties contrast with the anti-oestrogenic properties observed in the breast where SERMs inhibit the oestrogen-mediated development and growth of ER positive breast cancers. The two clinically useful SERMs, tamoxifen and its chemical cousin raloxifene, are currently used successfully either for the treatment and prevention of breast cancer (tamoxifen) or the treatment and prevention of osteoporosis (raloxifene). However, raloxifene has the beneficial side-effect of breast cancer prevention. These multifunction medicines provide proof of concept that novel molecules can be selectively targeted to diseases mediated by the endocrine system.
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Keywords: tamoxifen; raloxifene; selective oestrogen receptor modulator; breast cancer; chemoprevention; antioestrogen; osteoporosis; mammary cancer; arzoxifene

Abbreviations: ER, oestrogen receptor; HRT, hormone replacement therapy; SERM, selective oestrogen receptor modulator

It is less than 20 years ago that raloxifene (then known as keoxifene) was found to preserve bone density in the ovariectomized rat (Jordan *et al*., 1987), but also prevent the induction of rat mammary carcinogenesis (Gottardis and Jordan, 1987). These data catalysed the idea that non-steroidal antioestrogens (Jordan, 1984) were in fact selective oestrogen receptor modulators (SERMs) that were oestrogenic or antioestrogenic at different target sites around the body. The proposed application of this knowledge was to develop medicines to treat and prevent osteoporosis and to prevent breast cancer as a beneficial side effect (Jordan, 1988; Lerner and Jordan, 1990). The goal would be to develop a safer hormone replacement therapy (HRT). Traditional HRT, a mixture of orally active conjugated oestrogens and a synthetic progestin, is effective at preventing osteoporosis, but it is currently believed that the risks of developing an excess of breast cancer are unacceptable as a national health-care strategy (Million Women Study Collaborators, 2003).

The new SERM strategy has been successfully evaluated in clinical trials. Raloxifene dramatically reduces breast cancer incidence in postmenopausal women being treated for osteoporosis (Cummings *et al*., 1999; Martino *et al*., 2004). Additionally, raloxifene also reduces the incidence of breast cancer in high-risk women to the same extent as tamoxifen, that is about 50% (Vogel *et al*., 2006). However, although the translational research has effectively advanced therapeutics, questions now arise about optimizing the targeting of raloxifene to the breast. Raloxifene has a high binding affinity for the oestrogen receptor (ER) that is equivalent to that of oestradiol (Black *et al*., 1983), so the molecule should perform extremely well as an antioestrogen in the breast. Unfortunately, raloxifene appears to perform suboptimally. The goal of advancing therapeutics is to deliver the medicine to the right place at the right time; or in the case of breast cancer prevention – all of the time.

In this issue, Ning *et al*. (2007) study the structure–activity relationships and binding characteristics of raloxifene derivatives at their cognate receptors ERα and ERβ. What is encouraging is that a derivative of raloxifene called Y134 is identified, that appears to be superior to raloxifene with regard to mammary gland selectivity.

Raloxifene is an agent that was originally destined to be a drug to treat breast cancer, but it failed in that application (Buzdar *et al*., 1988). It appears that the pharmacokinetics and bioavailability of raloxifene are a challenge. Only about 2% of administered raloxifene is bioavailable (Snyder *et al*., 2000), but despite this, the drug is known to have a long biological halflife of 27 h. The reason for this disparity is that raloxifene is a polyphenolic drug, and this creates a complex dimension of glucuronidation and sulphation in the gut (Kemp *et al*., 2002; Jeong *et al*., 2005) which controls enterohepatic recirculation and ultimately prevents the drug from reaching the target. This concern has been addressed with the development of the long-acting raloxifene derivative arzoxifene that is known to be superior to raloxifene as a

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chemopreventive in rat mammary carcinogenesis (Suh *et al*., 2002). Nevertheless, arzoxifene has not performed well as a treatment for breast cancer (Baselga *et al*., 2003; Buzdar *et al*., 2003), but the results of trials evaluating the effects of arzoxifene as a drug to treat osteoporosis are eagerly awaited. Perhaps, arzoxifene will be a better breast cancer preventive than a treatment.

Unfortunately, keeping phenolic drugs in the target is another complication. 4-Hydroxytamoxifen, an active metabolite of tamoxifen (Jordan *et al*., 1977), is only sulphated by three of seven sulphotransferase isoforms, whereas raloxifene is sulphated by all seven (Falany *et al*., 2006). Maybe local phase II metabolism plays a role in neutralizing the antioestrogen action of raloxifene in the breast. Falany *et al*. (2006) further demostrate that SULT1E1 that sulphates raloxifene in the endometrium is only expressed in the secretory phase. In contrast, 4-hydroxytamoxifen is sulphated at all stages of the uterine cycle. If the emerging knowledge of this target site-specific phase II metabolism is applied to the breast, then perhaps an ideal agent can be designed to be retained in the breast and create optimal antioestrogenic activity. Studies such as those described by Ning *et al*. (2007) should be encouraged and expanded to identify specific SERMs, targeted to specific organs to treat and prevent numerous oestrogen-mediated diseases thereby improving women's health.

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