therapy, IMRT) or by using radioprotectors (amifostine?). Finally it remains to be tested in further studies what could be the optimal re-RT/CTschedule which would offer the best balance between tolerance and efficacy.

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The estrogen receptor as a target for breast cancer prevention

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The estrogen receptor (ER) is an important target for the modulation of estrogen action. Tamoxifen a non steroidal antiestrogen is the endocrine treatment of choice for all stages of breast cancer and the first drug available that reduces the incidence of breast cancer in high risk women. The advance was possible because tamoxifen selectively modulates ER action at different target sites i.e., it is estrogen-like in bone but antiestrogenic in breast. Additionally, tamoxifen causes a small increase in endometrial cancer incidence in postmenopausal women. Raloxifene, also an antiestrogen, has been developed for the prevention of osteoporosis but with anticipated breast and endometrial safety. It is currently being tested for the prevention of breast cancer and coronary heart disease. We have compared and contrasted the interaction of tamoxifen and raloxifene at ER alpha and found that whereas tamoxifen only silences activating function 2 (AF-2) raloxifene silences AF-1 and 2. data could explain the reduced estrogenity of raloxifene in uterus but other mechanisms need to be found to explain the estrogen-like effects of raloxifene on bone.

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Coactivators and hormone action

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Activation of transcription by nuclear receptors is potentiated by coactivator proteins which are recruited to the receptor in the presence of hormone. Hormone binding results in a conformational change in the receptor forming a novel surface to which coactivators may directly bind by means of leucine rich (LXXLL) motifs. Mutagenesis experiments on the oestrogen receptor (ER) have defined the major interaction site on the ligand binding domain consists of a hydrophobic groove flanked by conserved glutamic acid and lysine residues. Peptide competition studies demonstrate that residues N-terminal to the leucine motif are also involved in high affinity binding to the ER. In contrast, recruitment of the p160 protein SRC-1 to the androgen receptor occurs primarily by means of interactions between the N-terminal AF1 domain of the receptor and a glutamine-rich region in the. The role of the nuclear receptor interacting protein RIP140, which contains multiple LXXLL motifs, is being analysed in vivo following deletion of the gene in mice by homologous recombination. RIP140 is widely expressed in both embryonic and adult tissues and shows specific patterns of expression at different developmental stages. RIP140 (−/−) animals are viable and occur in a normal Mendelian ratio although show a reduction in growth compared to wild type and heterozygous controls. Female (−/−) mice are infertile while males, although fertile, die prematurely. The basis of these phenotypic changes is currently under investigation.

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Erβ – New development

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Estrogen signalling is complex and it has always been difficult to reconcile this fact with the textbook dogma that there only exists one estrogen receptor. (ER). Following our discovery of a second ER (Erβ), reported in 1996, views on estrogen mechanism of action have changed dramatically. Erα and Erβ appear to be quite distinct biologically and it may even be appropriate to describe their relationship as a yin-yang situation. Data from Erβ −/− mice show the following phenotypical characteristics: prostate hyperplasia; polycystic ovaries with follicular arrest (fertility is reduced by 80% in the females); lipodystrophy; defeminization of pubertal bone growth in females (i.e. -/- female mice are indistinguishable from wt and -/- male mice in that they do not show the usual slowing down of cortical bone growth typical of wt females during puberty); feminization (i.e. elimination of imprinting) of liver metabolism in -/- mice, indicating that these animals are not neonatally imprinted by estrogen at birth.

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Genetic dissection of glucocorticoid receptor function in mice

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Glucocorticoids are involved in numerous physiological processes. Most of the effects are thought to be mediated by the glucocorticoid receptor (GR) via activation and repression of gene expression. Activation requires binding of a receptor dimer while repression is mediated in many cases by protein-protein interaction of GR monomers with other transcription factors. To analyse glucocorticoid receptor function in vivo several mutations were generated in the mouse. Mice with a disrupted GR gene (null mutation) die shortly after birth due to respiratory failure indicating an important role of GR in lung function. To separate activating from repressing functions of the GR a point mutation in the D-loop of the receptor, which is required for receptor dimerization, was generated with a Cre-loxP based strategy. Mice carrying this point mutation (GR^{dim}) survive and allow to distinguish between GR functions dependent on DNA binding and those mediated by protein-protein interaction. Using cells from this mutant the molecular mechanism of cross-talk of GR with AP1 and NFkB was analyzed. Effects of glucocorticoids on AP1-controlled functions are not altered in GR^{dim} mice, suggesting that effects of GR on AP1 activity do not require DNA-binding. Further, DNA-binding-independent activity of the receptor is sufficient for immunosuppression in vivo. Since mice with a disrupted GR gene die after birth, cell-specific mutations have been generated with the Cre-loxP system. The GR gene was inactivated in liver, thymus and brain, respectively. Absence of GR in brain leads to alterations in control via the hypothalamic-pituitary-adrenal axis. The mutant mice appear to be less anxious revealing an involvement of GR in emotional behaviour and are impaired in learning and memory as shown in water maze studies. Mice deficient in GR function in liver and thymus are presently studied.

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New antioestrogens for breast cancer

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Considerable progress has been made in antioestrogen development recently. In the past most agents were based on the tamoxifen-like triphenylethylene structure and include toremifene, droloxifene, TAT-59 and idoxifene. The new or newly developed antioestrogens have novel structures and include the benzothiophenes, raloxifene and SERM III (Lilly), the benzpyran, 57050 (Schering) and the oestrogen analogue Faslodex (ICI 182780, Zeneca). It is likely that the new compounds will be more potent than the triphenylethylenes since preliminary evidence indicates that they are more efficient inhibitors of the oestrogen receptor (ER) in the breast and uterus. Whereas the triphenylethylenes block only one ER activating factor (AF2) at least two of the newer antioestrogens have been shown to block a second activating factor (AF1) thus inhibiting growth factor activation of ER. All four of the newer antioestrogens are in phase II or III clinical trial development: a summary of their activities will be presented.

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How to respond to complementary medicine: Introduction

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The use of complimentary medicine is increasing throughout Europe. This is partly a response to the wider availability of alternatives to conventional medicine, and partly due to disillusionment with the end results and morbidities associated with the use of conventional treatment.

This symposium will review the use of complimentary medicine in Europe, focusing on the availability of different types of complimentary medicine, the patient populations that use or seek advice about the use of complimentary medicine, and most particularly the attitude of the medical and nursing profession towards the use of complimentary therapies. There is only a small literature reporting attempts to scientifically validate the use of complimentary medicine, and the issues of whether or not it is possible to conduct unbiased clinical research in the field of complimentary medicine will be discussed.