ligand binding site and thus should not be blocked *in vivo* by the relatively high levels of human IgG. Her-2/*neu* is overexpressed in human breast carcinomas with poor prognosis. *In vitro* studies with MDX-210 have shown effective killing of tumor cell lines that express the HER-2/*neu* antigen. Eight patients have been treated to date. The dosage levels tested to date are 0.35, 1.0, and 3.5 mg/m^2 infused intravenously at 6.0 mg/hour. Infusion of MDX-210 has been well-tolerated by all patients. The principal toxicities have been Grade I/II fevers and malaise that have fully resolved by 12 hours post infusion. Evidence of immunological activity has been observed even at the lowest dose tested. Plasma tumor necrosis factor alpha (TNFα) increased to as high as 500 picogram/ml in 5 of 6 patients tested. Peripheral blood monocytopenia, either preceding or concurrent with elevations of plasma TNFα, is consistent with binding of MDX-210 to both immune effector cells and target breast tumor cells. Significant dose-dependent *in vivo* binding of MDX-210 to CD 64 has been observed for more than 24 hours post infusion. It has been demonstrated in cell culture studies that MDX-210 triggers release of TNFα from immune effector cells in the presence, but not in the absence, of target tumor cells. The observation that MDX-210 is immunologically active at non-toxic doses forms the basis for considering MDX-210 as a candidate chemotherapeutic drug for recurrent or secondary breast cancers.

Estradiol Metabolism: An Endocrine Biomarker for Chemoprevention of Human Mammary Carcinogenesis

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Abstract A relationship between altered metabolism of estradiol (E2) and personal or familial risk for breast cancer suggests that endocrine changes associated with ovarian function may influence initiation or promotion of carcinogenesis. Evidence for a direct effect of E2 on non-involved mammary tissue (target for carcinogenesis) is equivocal. Explant cultures of human mammary terminal duct lobular units (TDLU) from breast cancer patients are utilized to examine whether (i) E2 metabolism in TDLU is altered in response to the chemical carcinogen benzo(*a*)pyrene [B(*a*)P], and (ii) perturbed E2 metabolism is modulated by naturally occurring polyunsaturated fatty acids (PUFA) and indole-3-carbinol (I3C). Treatment of TDLU with 40 nM B(*a*)P resulted in a >95% decrease in C2/C16α-hydroxylation ratio of E2 relative to that detected in solvent controls. This metabolic alteration was due to a specific increase in E2 C16α-hydroxylation. Exposure of TDLU prior to and during B(*a*)P treatment with omega-6 PUFA **decreased** C2/C16α-hydroxylation ratio by 38% ($p < 0.001$). Treatment with omega-3 PUFA and I3C **increased** the ratio by 318% and 376% respectively ($p < 0.001$), due to a specific increase in E2 C2-hydroxylation. Thus, carcinogen-induced perturbation of E2 metabolism in TDLU and its modulation by dietary modulators of rodent mammary tumorigenesis provide evidence for this endocrine biomarker as a clinically relevant endpoint for chemoprevention of mammary carcinogenesis.

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