mammary cancer incidence in controls from 95% to 15%; carcinoma multiplicity in rats receiving 800 mg DHEA per kg diet was reduced by more than 85% from control levels. In a separate study, the 400 mg/kg diet dose of DHEA reduced the incidence of mammary cancer to 5% from 80% found in controls fed the basal diet. Reductions in mammary cancer incidence and multiplicity associated with DHEA administration were accompanied by large increases in cancer latency. Evaluation of mammary gland wholemounts from animals fed DHEA demonstrated a massive induction of lobuloalveolar differentiation. These results indicate the dietary supplementation with non-toxic dose levels of DHEA has chemopreventive efficacy approaching that of endocrine ablation. This protection may be mediated by the induction of differentiation in the mammary gland, during which sensitive mammary parenchymal structures (terminal end buds) are stimulated to develop into structures (alveolar buds) less sensitive to carcinogenic insult.

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Trapping of Genes Induced Upon Growth Arrest After Treatment With Antiestrogen or Retinoids Using Retroviral Promoter Trap

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Abstract Although chemopreventive anti-steroids such as the antiestrogens are thought to act through competitive inhibition of agonist binding to estrogen receptors, it has been postulated that the estrogen receptor changes its conformation when bound to a strong antiestrogen such as ICI-164,384. We hypothesized that such conformationally changed receptors could bind specific recognition sequences in the genome and activate specific genes that might be involved in growth arrest. In order to identify such genes with a functional assay, we used a retroviral gene trap U3*lac*Z. We have now isolated MCF-7 breast cancer cell line clones in which the *lac*Z reporter gene is inserted into the genes activated by either ICI-164,384 or retinoic acid. One such clone, B4, was further characterized. In B4, *lac*Z activity is induced by ICI-164,384 or *trans*-retinoic acid, and repressed after treatment with estradiol. Cloning of the 5'-flanking genomic sequence in this clone will be possible using polymerase chain reaction.

High Resolution Image Cytometry for Quantitative Assessment of Ductal Carcinoma *In Situ* of the Breast

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Abstract One of the most critical issues regarding management of early breast cancer is the proper detection and correct estimation of its malignant potential. In recent years, primarily through mammography, the frequency of ductal carcinoma *in situ* (DCIS) in malignant breast biopsies has increased several fold, from ~5% to over 20%. At present, DCIS classification is based exclusively on descriptive parameters and several attempts have been made to obtain uniform classification among pathologists. This goal has been elusive and further attempts both in North America and Europe have been made to better distinguish between DCIS lesions. However, even if this can be achieved to a satisfactory degree, the malignant potential of a DCIS lesion, either comedo or non-comedo, cannot be assessed without quantitative evaluation of these lesions. It may be possible to assess the malignant potential by estimating a variety of parameters, such as the presence of oncogenes or their products, presence of receptors, *etc.* To date, some of these have been shown either to be necessary or sufficient conditions for obtaining invasive cancer.

We have recently shown that the nuclear features of diagnostic cells, as well as nuclear features of the surrounding normal appearing cells, can be used for objective lesion classification and estimation of the malignant potential of DCIS lesions. A high resolution image cytometer (Cyto-Savant™, Xillix Technologies Corp.) has been developed. This device can be used for automated measurements of large numbers of cell nuclei stained stoichiometrically for DNA. Nuclear features such as size, shape, DNA amount, and foremost, the texture features describing the distribution of the DNA are extracted. The Cyto-Savant™ system has been trained to recognize the relevant cells in smears from fine needle aspirates or cytospins of cells extracted from tissue blocks using standard procedures. Several thousand cell nuclei per slide can be analyzed using only a few minutes of the pathologist's time. Combining qualitative assessment with quantitative data greatly improves the diagnosis of DCIS lesions and may provide prognostic and treatment monitoring information as well. The system will be discussed in detail and experimental data shown for several cases.

Bispecific Monoclonal Antibody Therapy (Anti HER-2/*neu* × Anti CD 64) for Human Breast Cancers That Overexpress HER-2/*neu*

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Abstract A Phase I clinical trial with a bispecific monoclonal antibody (BsAb) (anti HER-2/*neu* × anti CD 64) is currently being conducted in patients with Stage IV breast carcinoma or Stage III/IV ovarian carcinoma who are refractory to standard therapy and who overexpress the HER-2/*neu* antigen as determined by immunohistochemistry. The trial is a hybrid Phase Ia/Ib trial in which the principal endpoints are toxicity, determination of the maximum tolerated dose, biological efficacy, and BsAb pharmacokinetics. Clinical efficacy will be assessed employing standard cancer and leukemia group B (CALGB) criteria to categorize tumor responses. The BsAb, designated MDX-210, is a Fab′ × Fab′ construct which is designed to enhance tumor penetration owing to its relatively small molecular size (approximately 100 kD). CD 64 (FcγRI) is a high affinity Fc receptor for IgG and potent cytotoxic trigger molecule for monocytes, macrophages, IFN-γ-activated neutrophils, and G-CSF-activated neutrophils. The anti CD 64 employed in this study is uniquely constructed to bind to an epitope outside the normal