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Extracts prepared from primitive plant: common ladyfern (species Athyrium filix-femina) displays potent anti-cancer effects in preclinical assessments of diverse human malignant cell lines

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Research to be presented describes the potent anti-cancer properties of the common lady fern (plant Division Pterophyta, Family Dryoptheridaceae, species Athyrium filix-femina). This preclinical assessment has involved the determination that whole plant extracts prepared from this species (termed primiplex*™) induce cell death in diverse human solid tumor malignancies in vitro, among these, cell lines derived from cancers of the brain (glioblastoma), colon, lung, breast and several types of leukemia.

The plant extract formulations were prepared as whole plant homogenates in culture medium. Optimal dose range for the fern extract homogenate ranged from 200 microG per ml to 1mg over a time course of 24-48 hours for the preclinical assessments of anti-cancer activity in cell lines derived from several human solid tumor malignancies growing in culture either in the form of monolayers or as multicellular tumor spheroids. Cytotoxicity assays involved the standard trypan blue exclusion assay as well as survival assays to assess post-treatment culture viability. The results of these preliminary assessments suggested that the extract formulation displays potent anti-cancer properties with broad spectrum cytotoxic potential against human cancers of diverse tissue origins.

Combined treatment studies involving the use of the plant extract with standard cancer therapeutics showed that this extract may enhance the efficacy of standard treatment regimens, in that enhanced cytotoxicity was observed when the extract was combined with:

- Vinblastine in acute lymphoblastic leukemia and chronic myelogenous leukemia;
- Fluorouracil in primary and metastatic colon carcinoma
- Tamoxifen in estrogen receptor positive and negative breast cancers.

To our knowledge, this is the first documented assessment of the anti-cancer properties of this group of primitive plants. Moreover, these studies suggest that the anti-cancer properties of the primitive plant extract may be preventive as well as therapeutic. In addition, this research defines a preparative formulation of the whole plant that preserves its anti-cancer properties. Confocal laser microscopy imaging studies suggest that an important target of these plant extract preparations is the actin cytoskeleton.

*Patent pending, ™ 2008

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The effect of the synthetic estrogen – diethylstilbestrol (des) and indol-3-carabinol(i3c) on the distribution of telomerase expression cells in lines of prostate cancer

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Background: Expression of telomerase is an essential step in cancer cell immortalization and progression. Modulation of its expression may be beneficial for controlling cancer cell proliferation. Prostate cancer patients are treated with estrogens in order to abolish testicular androgen formation. Studies with the phytochemical Indol-3-Carbinol (I3C) have shown its anti-proliferation capabilities.

Objective: Flow cytometry was used to examine the effect of the synthetic estrogen- Diethylstilbestrol (DES) and I3C on the distribution of telomerase expressing cells in two cancer prostate cell lines (PC3 - androgen insensitive) and LNCaP

Results: Regarding fluorescence intensity of the two lines, three subgroups of cells, with low, medium and high intensities (A,B and C respectively), were demonstrated. Group C consisted of about 2% of the cells of both lines while A and B included all the rest. DES and I3C had no effect on groups A and B of both lines. While group C, although minor, was the only one, in both lines, responding to the added compounds: As to DES, concentrations of 25 and 50μM, increased the LNCaP group C to 11.8% and 6.2% of the cell population, whereas, in PC3, to 7.78 % and 4.4% respectively. Contrary to DES, I3C showed an inhibitory effect on C groups of both lines. An inhibition of 83.6% was obtained with the LNCap line treated with a combination of 25μM Des and 250μM 3IC, and 80.6% with PC3 treated with 25μM Des and 250μM 3IC.

Conclusions: The present results emphasizes an occult possible oncogenic characteristic of DES which was attenuated by I3C. We wonder whether Indol could be beneficial for treatment of prostate cancer.

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Quercetin, luteolin and ursolic acid are potent inhibitors of proliferation in colorectal carcinoma cells: new therapeutic tools?

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PI3K/Akt and MAPK/ERK signalling pathways play critical roles in cell proliferation and survival. Components of these pathways are often altered in colorectal carcinoma (CRC) where they increase proliferation and confer drug resistance. These pathways, therefore, have received increasing attention as targets for cancer therapy. Several dietary phytochemical constituents have been shown to have anti-cancer effects by inhibiting proliferation and inducing apoptosis in cancer cells. The aim of our study is to investigate the effect of luteolin (Lut), quercetin (Que) and ursolic acid (UA) on cell proliferation through PI3K/Akt and MAPK/ERK pathways in the CRC derived cell lines HCT15 and CO115.

Both cell lines were treated with different concentrations of compounds and significant inhibition of proliferation was observed using the BrdU incorporation assay. Western blotting analysis showed that Lut and Que inhibited ERK phosphorylation in HCT15 cells which have a RAS mutation. In CO115 cells that overexpress Akt, but have no RAS mutations, Que, Lut and UA inhibited phospho-Akt but not phospho-ERK. We find that the effect of the compounds depend on the genetic background of the cell lines. In addition, these effects were more pronounced than those obtained for wortmannin and PD-98059, reference inhibitors of PI3K and MEK, respectively. These results suggest that these compounds might be interesting to test in combination with classical chemotherapy drugs in order to enhance the effects of these drugs, and decrease chemoresistance.

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Combination of different agents against ErbB receptors significantly reduce SKBR3 breast cancer cell line proliferation

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Background: The epidermal growth factor receptor (EGFR) or ErbB family consists of four closely related tyrosine kinases: ErbB-1 (EGFR), ErbB-2 (HER2), ErbB-3 (HER3) and ErbB-4 (HER4). The association of ErbB members with breast cancer development has been extensively described in literature. EGFR, ErbB-2, and ErbB-3 are frequently overexpressed in breast cancer and negative regulation of them results in an inhibition of cell proliferation and spreading. Optimal use of therapeutics targeting these receptors require further identifying the contribution of ErbB family to tumorigenesis and interactions between all their members.

This study was focused on the effect of different ErbB inhibitors on proliferation of SKBR3 breast cancer cell line. We examined antibody Herceptin®, tyrosine kinase inhibitor (TKI) erlotinib, and siRNA against ErbB member as a single agent or in combination.

Materials and methods: Flow cytometry, light microscopy, western blot and viability/cytotoxicity tests were used for evaluation of the cell growth, ErbB pathway activation and protein expression, percentage of apoptotic cells and morphological features of cell death.

Results: Our study confirmed that the downregulation and/or inhibition of EGFR, ErbB2 and ErbB3 significantly reduce proliferation of SKBR3 breast cancer cell line. This effect depends on combination of agents, doses and time of exhibition.

Conclusion: We propose that using three agents against ErbB proteins with different mechanism of action may be valuable and innovative tool in breast cancer therapy.

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Active p53 contributes to antitumor effects of cyclin-dependent kinase roscovitine in multiple myeloma cells

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Small molecule inhibitors of cyclin-dependent kinases (CDK) are considered to be potential anticancer agents. Our previous work recently resulted in an identification of olomoucine II, a compound structurally similar to roscovitine (CYC202, seliciclib), which currently undergoes clinical evaluation as an anticancer drug. Both roscovitine and olomoucine