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CHEMOPREVENTION OF MAMMARY CARCINOGENESIS BY SYNTHETIC ANALOG OF VITAMIN D5.

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In order for vitamin D to be active, it needs to get metabolized to 1,25 $(OH)_2$D3. This active metabolite of vitamin D induces epithelial cell differentiation and is antiproliferative. However, at the efficacious concentration, the natural ligand for VDR is hypercalcemic and toxic to cells. Therefore, numerous analogs have been synthesized with the hope of generating a compound that retains vitamin D activity and is non-toxic. We synthesized such an analog 1α-hydoroxy-24-ethylcholecalciferol (1α(OH)D5) and showed that it was tolerated by rats and mice at a concentration 50 times greater than 1α,25$(OH)_2$D3. This property makes it a prime candidate for prevention studies. The chemopreventive efficacy of 1α(OH)D5 was evaluated in the MNU-induced rat mammary carcinogenesis model. Sprague/Dawley female rats at 100 days of age received 50mg/kg MNU and were treated with dietary intervention of either 25 or 50μg/kg 1α(OH)D5 in diet. Results showed statistically significant reduction of tumor incidence and tumor multiplicity at higher dose of vitamin D with no effect on plasma calcium concentration. In order to determine if the effect of vitamin D is selective in preventing cell transformation or suppressing proliferation of transformed cells, two studies were conducted. The effects of 1α(OH)D5 on cell growth and cell cycle arrest were compared between MCF12F (normal human breast epithelial cells) and BT474 (breast cancer) cells. Results showed that 1α(OH)D5 induced apoptosis and cell cycle arrest in G1 phase only in the ER+, VDR+ breast cancer cells without having any effect on cell proliferation of the normal cells. It was ineffective against VDR-, ER- MDA-MB-231 breast cancer cells. These results suggested that 1α(OH)D5 action probably is mediated by VDR and may interact with estrogen inducible genes. In the present study,

the effects of 1α(OH)D5 were also determined on estrogen responsive progesterone receptors. Immunocytochemical studies showed that 1α(OH)D5 suppressed progesterone receptor expression in BT474 cells. To further establish the selectivity of vitamin D action, we determined effects of 1α(OH)D5 in explant culture of normal breast and tumor tissues obtained after surgery. It was observed that 1α(OH)D5 at non-toxic 1μM concentration induced apoptosis and suppressed Ki-67 immunoreacivity in tumor tissues without affecting the epithelial cells of normal breast. These results collectively indicate that 1α(OH)D5 at non-toxic concentration selectively induces apoptosis in transformed cells and not in normal breast epithelial cells. We are currently in the process of developing this agent for Phase I/II clinical trials. (Supported by NCI CA-82316, and DOD 17-99-1-9223)