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Low-Calcemic Vitamin D Analogs (Deltanoids) for Human Cancer Prevention

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This article very briefly highlights some recent advances in cancer chemoprevention using various vitamin D analogs (deltanoids) (1). Epidemiological studies have shown that high levels of dietary intake of vitamin D and/or sunlight-induced formation of vitamin D in human skin correlate with lower incidence of cancer. This inverse relationship between high vitamin D levels and low cancer levels in human populations is best documented for colon and colorectal cancers (2,3). Clinical use of supraphysiological levels of the vitamin’s hormonally active form 1α,25-dihydroxyvitamin D [1α,25(OH)2D3, calcitriol], however, is seriously limited by toxicity (hypercalcemia) (4,5). Therefore, international effort has been devoted to designing, synthesizing and evaluating new deltanoids that have low calcemia-inducing activities and yet are effective cancer chemopreventive agents. Figure 1 shows the chemical structures of the most successful of such deltanoids for cancer chemoprevention (the boxed units emphasize where structural modifications have been made). In all of these designer deltanoids, considerable skill and effort were needed to design and to synthesize the requisite chemical building blocks with which to assemble the structurally and stereochemically complex target deltanoids. Major pharmaceutical companies such as Chugai (Japan), Leo (Denmark), and Hoffmann-La Roche (United States) have major roles in this area.

The first deltanoid in Figure 1 differs from the natural hormone 1α,25(OH)2D3 by lacking a 25-OH group and by having an extra ethyl group at C-24. This Moriarty deltanoid is about fourfold less calcemic than the natural hormone and has been shown to be efficacious in preventing tumor formation in an in vivo xenograft cancer model (6,7). A major review of this subject appeared in 2001 (8) and therefore the following discussion is limited to the Hopkins-QW-1624F2-2 deltaxanoid.

As the only deltaxanoid in the accompanying figure that was designed, prepared and evaluated in a university laboratory rather than in a pharmaceutical company, Hopkins-QW-1624F2-2 is a hybrid analogue designed rationally to incorpo-
rate two different structural modifications: i) an extra CH₂ unit between the 1-position and the natural 1-OH group to minimize calcemic activity and ii) a 16-ene 24-fluorinated side chain to potentiate antitumor activity while being only slowly metabolized (9). Despite the absence of the natural 1α-OH in hybrid deltanoid Hopkins-QW-1624F₂-2, its vitamin D receptor mediated transcriptional activity (ED₅₀ = 5 × 10⁻¹¹ M) in rat osteosarcoma ROS 17/2.8 cells exceeds that of the natural hormone 1α,25(OH)₂D₃ (ED₅₀ = 3 × 10⁻¹⁰ M) (9). A skin cancer chemoprevention study using this hybrid deltanoid was performed recently in female CD-1 mice initiated with DMBA and promoted biweekly for 20 wk with TPA (10). Topical application of deltanoid Hopkins-QW-1624F₂-2 (3 μg/mouse) 30 min before each TPA application significantly enhanced tumor latency in addition to reducing tumor incidence by 28% and tumor multiplicity by 63%. Unlike natural 1α,25(OH)₂D₃ at this dose, hybrid deltanoid Hopkins-QW-1624F₂-2 did not adversely affect body weight gain in these animals. Moreover, no increase in urinary calcium excretion was observed after this chronic treatment with Hopkins-QW-1624F₂-2, a result consistent with our observation that this deltanoid is 100-fold less calcemic than calcitriol (9).

With support by the U.S. Natural Cancer Institute (RAPID program) of the National Institutes of Health, scale-up synthesis of Hopkins-QW-1624F₂-2 is now being completed. Thus, milligram samples of this fascinating deltanoid should soon be available to the general scientific community upon request for preclinical toxicology and pharmacology testing, we hope in direct head-to-head tests with other leading deltanoids, for cancer prevention as well as cancer chemotherapy.

LITERATURE CITED