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The research in Dr. Thomas Slaga's laboratory is focused on glucocorticoid hormones (GC), very potent inhibitors of physiological DNA synthesis in keratinocytes *in vivo*. These hormones are also very effective in preventing carcinogen- and tumor promoter-induced skin hyperplasia, inflammation, and mouse skin tumor formation when applied to skin together with a carcinogen or a tumor promoter. We and others have shown, however, that the GC do not affect the growth of either established papillomas, squamous cell carcinomas (SCC), or transformed keratinocytes *in vitro*. In addition, we recently found that the GC do not affect glucocorticoid-responsive genes in transformed keratinocytes both *in vitro* and *in vivo*. We have generated skin-targeted transgenic mice over-expressing the GR under the control of the keratin 5 (K5) promoter. These adult transgenic mice have impaired proliferative and inflammatory responses to skin tumor promoters. Our initial studies showed that the K5.GR transgenic animals are resistant to *ras*-induced tumorigenesis. The constitutively nuclear overexpression and activation of the GR in the epidermis dramatically inhibited skin tumor development in K5.GR/*ras*+ double transgenic mice in terms of number of animals that develop tumors, number of tumors per animal, and tumor size. In another study we plan to determine the mechanism(s) of synergistic action of the natural source compounds, known to inhibit one or more stages of skin carcinogenesis, *i.e.*, initiation and promotion/progression. The concurrent topical and systemic (*i.e.*, dietary) treatment with selected natural source inhibitors of different stages of skin carcinogenesis result in synergistic effects leading to more efficient prevention of skin cancer. The natural source inhibitors to be tested include ellagic acid, imperatorin from the family of coumarins, proanthocyanidin B-2-gallate, (-)-epigallocatechin from the family of green tea polyphenols, N-acetylcysteine, calcium D-glucarate, lycopene, carnosol and ursolic acid from rosemary extract, and resveratrol. We propose to initially utilize a number of very predictive short-term *in vitro* and *in vivo* tests in order to identify the

mechanism(s) and to differentiate the potencies of selected inhibitors at various concentrations under standard conditions. The most effective compounds will then be studied in long-term tumor experiments utilizing a 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted multistage carcinogenesis model in SENCAR mice. Garcia GE, Wisniewski HG, Lucia MS, Arevalo N, **Slaga TJ**, Kraft SL, Strange R, Kumar AP. 2-Methoxyestradiol inhibits prostate tumor development in transgenic adenocarcinoma of mouse prostate: role of tumor necrosis factor- $\alpha$ -stimulated gene 6. **Clin Cancer Res.** 12:980-988, 2006.

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