

I am writing to request an opportunity to make a formal oral presentation at the Pediatric Advisory Committee meeting on February 15, 2005, on the subject of topical dermatological immunosuppressants. I would like 10 minutes to speak.

My name is Daniel B. Yarosh, Ph.D. and I am President and Chairman of Applied Genetics Inc. Dermatics, a New York biotechnology small business. My fields of training and expertise over 25 years are molecular biology, photobiology and DNA repair.

Our laboratory is studying the effect of calcineurin inhibitors, such as cyclosporine A, ascomycin, tacrolimus and pimecrolimus, on repair of UV-induced DNA damage. Our company has no direct commercial interests in these drugs and our research described here is not supported by any outside government or commercial entity.

We have found that cyclosporine A and ascomycin both reduce DNA repair after UVB irradiation in skin cells, and also inhibit apoptosis after UVB. In addition, they both inhibit UV-induced apoptosis. These effects are observed at physiological doses of drugs and UV light. Since these drugs are dissimilar but share the same target (calcineurin), we suggest that these effects are due to inhibition of calcineurin. The persistence of DNA damage and the loss of apoptosis in skin cells are well-documented early steps leading to skin cancer.

Systemic use of calcineurin inhibitors greatly increases the rates of skin cancer in sun exposed skin of organ transplant patients. A published study of mice treated with the carcinogen DMBA showed that topical application of the calcineurin inhibitor tacrolimus greatly accelerated skin cancer formation. Only one photocarcinogenesis study was submitted in support of either topical tacrolimus or topical pimecrolimus at the time of drug approval, and in each case it was flawed because the vehicle alone had a large carcinogenic effect. Published human safety studies of tacrolimus and pimecrolimus are too short (one year) and inadequately designed and powered to detect a change in skin cancer rates.

Increased DNA damage burden in children is of particular concern since they have much longer time than adults for these persistently damaged cells to transform into skin cancer. Epidemiological studies have shown that a significant risk factor for skin cancer in adults is the amount and type of sun exposure as children.

The label warning to “avoid natural or artificial sunlight” inadequately describes the risk of skin cancer to physicians, parents and patients.

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