**Effects of imiquimod treatment on experimental melanoma**

Ruth Camargo Vassao[1], Pamela Oliveira Souza[2], Cyro-Festa Neto[3], Durvanei Augusto Maria[2].

[1] Lab. Genética, Instituto Butantan - Av. Vital Brasil, 1500 055-900 São Paulo–SP

[2] Lab. Bioquímica e Biofísica, Instituto Butantan

[3] Dep. Dermatology, HCFMUSP Universidade de São Paulo, São Paulo, Brazil.

Imiquimod is the first of a new class of immune response modifying drugs for the treatment of genital warts, in a variety of dermatological conditions, such as basal cell carcinomas and actinic keratoses (premalignant intraepidermal keratinocyte neoplasias). In clinical trials, Imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine), a topical compound of Mr=240.3, has demonstrated high efficacy in the treatment of neoplasias. Clinical observations also indicate that Imiquimod may be efficacious for topical treatment of some melanoma metastases. It is thought that Imiquimod exerts its effect through elicitation of a strong cell-mediated antitumoral immune response. Its action is mediated, at least in part, through TLR-7-dependent regulation of the transcription factor NFKB, which upon activation migrates to the nucleus and upregulates transcription of various cytokines. In addition, Imiquimod activates dendritic cells possibly resulting in prolonged protective Th1-skewed immunity against viral infections and malignant tumors, and has shown direct pro-apoptotic activity towards epithelial cancer cells. In this work, groups of five C57BL/6J mice were s.c. injected with $5x10^4$cells of B16F10 murine melanoma. Tumor growth was measured and observed weekly, and tumor volumes were calculated using the following formula: (length) x $(width)^2$ x (□/6). After 10 days, the animals bearing dorsal tumors were treated daily with topical application of Aldara (IMIQUIMOD - 5% cream). Saline-treated animals were used as controls. The animals were weighed and the area and tumoral

volume were measured for 14 days. Our results indicate significant ($p<0.01$) reduction in the mass and tumoral volume of the treated animals. The treated group presented significant increase in the survival rate (8 days). Alteration weight loss of the treated animals was not observed when they were compared with the control group, which presented increased caquexia and accented mortality. Imiquimod-treated tumors showed decreased malignant cell proliferation, tumor burden and increased survival. We also observed an intense and significant peritumoral infiltrate of mononuclear leukocytes, without histological alterations in other organs. The results demonstrated that local application of Imiquimod inhibits the proliferation of the melanoma tumor model suggesting a novel and less toxic means to eradicate melanoma and other cancers.

Key words: melanoma, tumor, immunomodulation, cell proliferation