Histamine $H_4$ Receptor Ligand JNJ7777120 Inhibits Lung Metastases in MDA-MB-231 Xenograft Tumor-bearing Mice

Vanina A Medina$^{1,2}$, Maximo Croci$^3$, Graciela P Cricco$^1$, Ernesto JV Crescenti$^2$, Rosa M Bergoc$^{1,2}$, Elena S Rivera$^1$

$^1$Laboratorio de Radioisótopos, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, 1113, Argentina
$^2$Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina
$^3$Instituto de Inmunoncología, Av. Córdoba 3200, Buenos Aires, 1187, Argentina

We have recently reported the presence of histamine $H_3$ ($H_3R$) and $H_4$ ($H_4R$) receptors in benign and malignant lesions of the human mammary gland with the level of their expression significantly higher in carcinomas. 50% of malignant lesions expressed $H_4R$, all of them corresponding to metastases or high invasive tumours. In addition, we showed the expression of $H_3R$ and $H_4R$ in breast cell lines and we found that they are the main receptors responsible for the histamine-mediated responses such as proliferation, apoptosis and migration; in MDA-MB-231 cells.

The aims of the present study was to determine the expression of $H_4R$ and to examine the effect of the compound JNJ7777120 on the survival, tumor growth rate, metastatic capacity and molecular pattern of expression of breast cancer in vivo. For that purpose, we established orthotopic xenograft tumors of the highly invasive human breast cancer line MDA-MB-231 in immune deficient nude mice.

Results indicate that the $H_4R$ was the major histamine receptor expressed in the xenograft tumors that also exhibited high levels of histidine decarboxylase (HDC), histamine content and proliferation markers. Mice of untreated group displayed a median survival of 60 days, and a tumor doubling time exponential growth of 8 days. Developed tumors were highly undifferentiated and invasive and 90% of animals exhibited several ganglionary and lung metastases. JNJ7777120 treatment, which was daily administered orally (10 mg/Kg), completely inhibited lung metastases while did not modify significantly survival or tumor growth rate. Tumours from treated animals showed a reduced expression of $H_4R$ and HDC.

This preliminary report describes that JNJ7777120 is capable of abolishing lung metastasis offering a novel therapeutic potential of this $H_4R$ ligand for breast cancer treatment.

We thank Dr. Nicholas Carruthers from Johnson & Johnson Pharmaceutical Research & Development for the compound JNJ7777120.