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

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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 decarboxilase (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.

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