New and powerful NHE1 inhibitors as potential anticancer drugs in bedside oncology: A prospective program of preclinical studies in cats and dogs with spontaneous malignant tumors

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Background and aim. The utilization of different proton transport inhibitors (PTIs) to inhibit NHE1 as an anticancer target have been increasingly proposed as a novel approach to the pH-related treatment of cancer by different research groups (1-3). We initially conducted a preliminary clinical trial in patients with advanced malignant tumours using a concerted cocktail of several commercially available PTIs, obtaining some hopeful initial results (4). From the therapeutic point of view, the final aim would be to revert proton reversal and/or the Warburg effect by selective intracellular acidification while at the same time decreasing the extracellular acidification of malignant tumours, a feature that is known to actively involved both in local growth and in the metastatic process. Unfortunately, the most potent and selective NHE1 inhibitors of the amiloride and non-amiloride series such as cariporide, Phx-3 (2-aminophenoxazine-3-one) (1) and compound 9t (a 5-aryl-4-(4-(5-methyl-1H-imidazol-4-yl)piperididn-1-yl)pyrimidine analog (5) still need to be included in further pre-clinical and clinical trials as an important part of a new paradigm in the anticancer medical armamentarium. These compounds, alone or in combination, could be most useful either as chemotherapeutic agents on their own, in the context of preventing and controlling the metastatic process and/or in any attempts to reverse multiple drug resistance (MDR), at least in NHE1-upregulated malignant tumors.

Material and Methods. We have recently initiated a preclinical research and therapeutic program in dogs with spontaneous breast cancer and lymphomas and cats with spontaneous lymphomas in order to test the feasibility, anticancer effects and possible side-effects of some the most potent PTIs and selective NHE1 Inhibitors known to date.

Results. Both cariporide and Phx-3 have shown no side-effects used in increasing dosages by oral administration during periods of at least three weeks. No matter that this program has been initiated most recently, preliminary results will be presented.

Conclusions / Discussion. Cariporide, as well as the new and powerful and selective NHE1 inhibitors of the non-amiloride series, like Phx-3 and compound 9t, represent a new and so far minimally explored paradigm in preclinical studies and bedside cancer therapeutics.

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