Antitumor properties of histamine *in vivo*

To the Editor:

Yang *et al.*[1] recently reported that mice with histamine deficiency due to genetic disruption of histidine decarboxylase (HDC) show impaired myeloid cell differentiation. The absence of histamine formation caused accumulation of immature myeloid cells (IMCs), which was accompanied by an increased susceptibility to chemically induced cancer[1]. Exogenous histamine reversed the accumulation of tumor-promoting IMCs in *Hdc*$^{-/-}$ mice, suggesting a potential benefit of histamine-based therapy in cancers[1], where IMCs are believed to contribute to an unfavorable course of disease[2]. Given the effect of exogenous histamine on IMCs, we were surprised that the authors did not discuss the *in vivo* effects of histamine on cancer development in animals. As seen in **Table 1**, histamine is an antitumor agent in several histiotypes of experimental cancer[3–7].

The authors also did not mention that histamine has been evaluated in clinical trials in cancer as an inhibitor of immunosuppressive myeloid cells[8]. In metastatic renal cell carcinoma, the addition of histamine to interleukin-2 immunotherapy was reported to reduce the number of intratumoral macrophages[9], implying an effect on the myeloid compartment resembling the results obtained by Yang *et al.*[1]. Furthermore, histamine is approved for use in 31 European countries and Israel to prevent relapse in acute myeloid leukemia (AML), a disease characterized by the accumulation of immature myeloid cells. The therapeutic use of histamine in AML aims to reduce myeloid cell–induced immunosuppression of cytotoxic lymphocytes[8,10]. In light of these previous findings, and considering the results presented by Yang *et al.*[1], further studies to define mechanisms of relevance to the antitumor properties of histamine *in vivo* seem highly warranted.

Fredrik B Thoren[1,2], Johan Aurelius[2] & Anna Martner[2]

[1]Department of Hematology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. [2]Cancer Centre Sahlgrenska, University of Gothenburg, Gothenburg, Sweden.
e-mail: fredrik.thoren@gu.se

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Yang, X.D. *et al. Nat. Med.* **17**, 87–95 (2011).
2. Gabrilovich, D.I. & Nagaraj, S. *Nat. Rev. Immunol.* **9**, 162–174 (2009).
3. Burtin, C., Scheinmann, P., Salomon, J.C., Lespinats, G. & Canu, P. *Br. J. Cancer* **45**, 54–60 (1982).
4. della Rovere, F., Broccio, G., Granata, A. & Fimiani, V. *Oncol. Rep.* 1, 175–177 (1994).
5. Suonio, E., Tuomisto, L. & Alhava, E. *Agents Actions* **41** Spec No, C118–C120 (1994).
6. Tatsuta, M. *et al. J. Natl. Cancer Inst.* **76**, 277–281 (1986).
7. Hellstrand, K. *Semin. Oncol.* **29**, 35–40 (2002).
8. Martner, A. *et al. Expert Rev. Hematol.* **3**, 381–391 (2010).
9. Donskov, F., Hokland, M., Marcussen, N., Torp Madsen, H.H. & von der Maase, H. *Br. J. Cancer* **94**, 218–226 (2006).
10. Brune, M. *et al. Blood* **108**, 88–96 (2006).

Table 1 Histamine in experimental cancer

Research group	Histiotype	Effect of histamine
Burtin *et al.*[3]	Fibrosarcoma	Inhibition of tumor growth and prolonged survival in mice
Tatsuta *et al.*[6]	Intestinal adenocarcinoma	Reduced incidence of chemically induced tumors in the small intestine in rats
Hellstrand *et al.* (reviewed in ref. 7)	Melanoma	Prevention of melanoma metastasis formation in mice
Suonio *et al.*[5]	Colorectal carcinoma	Reduction of tumor size of transplanted human colon carcinoma cell in mice
della Rovere *et al.*[4]	Ascitic sarcoma	Protection of 80% of mice from a lethal inoculum of sarcoma cells
Asea *et al.* (reviewed in ref. 7)	Lymphoma	Enhanced clearance of YAC-1 lymphoma cells in mice

Yang and Wang reply:

We would like to thank Thoren *et al.*[1] for their comments on our recent study[2] and for highlighting important previous preclinical and clinical studies on the effects of histamine in cancer. Indeed, we did not have the space to cite the many excellent prior research efforts that have employed histamine or histamine receptor antagonists as antitumor agents. We are grateful to Thoren *et al.*[1] in particular for calling to our attention the fact that histamine has been approved in Europe and Israel for treatment of AML[3,4]. Nevertheless, the effects of histamine in cancer models are often paradoxical, and the mechanisms for the antitumor effects of histamine have in the past been unclear. Histamine has multiple physiological roles and targets; we are aware of other earlier literature that suggested direct effects of histamine on cancer cell growth, and a number of preclinical studies have shown antitumor effects of H_2 receptor antagonists[5,6]. In addition, whereas Martner *et al.*[7] suggested that histamine is an inhibitor of immunosuppressive myeloid cells, our studies in mice indicate that the effect is primarily on both CD11b$^+$Ly6G$^+$ and CD11b$^+$Ly6C$^+$ immature myeloid cells (IMCs), and the latter are suggested to be the major suppressor population[2,8]. Nevertheless, work from us and them is consistent with the conclusion that histamine seems to reduce the mobilization and circulating numbers of myeloid cells and inhibit progression of some types of cancer[9]. We agree that further studies are needed to define the effects of histamine in the regulation of myeloid differentiation and maturation, which seems to be central to the promotion of cancer.

Xiang Dong Yang & Timothy C Wang

Division of Digestive and Liver Diseases, Department of Medicine and Irving Cancer Center, Columbia University, New York, New York, USA.
e-mail: tcw21@columbia.edu