

# This Week's Citation Classic

Hellström I, Hellström K E, Sjögren H O & Warner G A. Demonstration of cell-mediated immunity to human neoplasms of various histological types. *Int. J. Cancer* 7:1-16, 1971. [Depts. Microbiol. and Pathol., Univ. Washington Med. Sch.; Dept. Immunol., Fred Hutchinson Cancer Ctr.; and Swedish Hosp. Tumor Inst. and Med. Ctr., Seattle, WA]

**Peripheral blood lymphocytes from 51 of 59 cancer patients were found to react *in vitro* to autochthonous tumor cells, as were lymphocytes from 78 of 87 patients when tested on allogeneic tumor cells of the same histological type as that of the lymphocyte donor. Evidence for shared tumor antigens was obtained for seven different tumor groups, including melanomas and carcinomas of the colon and breast. [The SC<sup>i</sup>® indicates that this paper has been cited over 720 times since 1971.]**

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"A group headed by us had published, in 1968, that lymphocytes from some cancer patients inhibit (or kill) plated tumor cells from the respective patients or from other patients with the same type of tumor.<sup>1</sup> We tried to extend this work when Hans Olov Sjögren (the brother of Ingegerd Hellström and now a professor at the University of Lund, Sweden) spent two years in Seattle around 1970. The 1971 paper presents our findings.

"Our results were unexpected: not only did we observe that tumors of the same type share antigens but also that lymphocytes from patients with growing tumors can be as reactive as are lymphocytes from patients whose tumors have been removed. We believed that the shared antigens were differentiation antigens,<sup>2</sup> and attributed the growth of tumors in the face of an immune reaction to serum factors suppressing ('blocking') lymphocyte reactivity.

"The major reason why our paper has been much cited is that it provides some of the first evidence that common human tumors (eg., carcinomas of the colon and breast) can be recognized as foreign by the host. The paper has also been controversial, which contributes to the many citations, too. Part of the controversy is due to the fact that we had postulated that the shared tumor antigens might be suitable targets for diagnostic and therapeutic procedures — 'spontaneous' human tumors were thought not to express any such antigens. The fact that many colleagues had difficulties reproducing our results did not help the matter. In retrospect we believe that the conflict of findings had a technical explanation: we had worked with tumors of short *in vitro* passage and patients only treated with surgery, and we had exposed the target cells to lymphocytes for two to five days, while the work of many colleagues was carried out slightly differently. Destruction of tumor cells by NK (natural killer) cells present in all lymphocyte populations was what was primarily observed in their studies.

"Are the conclusions of our 1971 paper valid today? We think so. Findings with the leukocyte migration and adherence inhibition techniques have confirmed the presence of shared antigens in tumors of the same type,<sup>3</sup> and monoclonal antibodies to type specific differentiation antigens have been recently raised.<sup>4</sup> Indeed, the diagnostic and therapeutic procedures hinted at in our 1971 paper now attract much attention, using monoclonal antibodies as tools. Even the postulated serum factors are well established—in the form of tumor antigens and complexes activating suppressor T cells (which in their turn form suppressor factors).<sup>3</sup>

"Thus we feel happy about our 1971 paper. Of course, we would have felt even happier, had we realized then that what was attributed to 'cell-mediated tumor immunity' encompassed several mechanisms (T cell killing, ADCC, NK effects) and that the 'tumor specificity' of most shared differentiation antigens is relative rather than absolute "

1. Hellström I, Hellström K E, Pierce G E & Yang J P S. Cellular and humoral immunity to different types of human neoplasms. *Nature* 220:1352-4, 1968.
2. Hellström I, Hellström K E & Shepard T H. Cell-mediated immunity against antigens common to human colonic carcinomas and fetal gut epithelium. *Int. J. Cancer* 6:346-51, 1970.
3. Hellström K E & Brown J P. Tumor antigens. (Sela M. ed) *The antigens*. New York: Academic Press. 1979 Vol. 5. p. 1-82.
4. Herlyn M, Steplewski Y, Herlyn D & Koprowski H. Colorectal carcinoma-specific antigen, detection by means of monoclonal antibodies. *Proc. Nat. Acad. Sci. US* 76:1438-42, 1979.