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This Week's Citation Classic®

Rosenberg S A, Lotze M T, Muul L M, Leitman S, Chang A E, Ettinghausen S E, Matorj Y L, Skibber J M, Shiloni E, Vetto J T, Seipp C A, Simpson C & Reichert C M. Observations on the systemic administration of auiologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N. Engl. J. Med.* 313:1485-92, 1985. [National Cancer Institute and Clinical Center. National Institutes of Health. Bethesda. MD]

Patients with advanced cancer that had failed standard treatments received intravenous injections of lymphokine-activated killer cells and interleukin-2 (IL-2). Objective cancer regressions were seen in selected patients. This paper was the first to describe.the mediation of cancer regression in humans by an IL-2 based immunotherapy. [The *SCI*® indicates that this paper has been cited in more than 1,085 publications.]

The Development of Immunotherapy for Cancer

Steven A. Rosenberg
National Cancer Institute
Bethesda, MD 20892

Two patients that I encountered early in my surgical training influenced me to attempt to develop immune approaches to the treatment of patients with cancer. One patient had received a kidney transplant that unknowingly contained a cancer. The transplanted cancer spread to the lungs but was completely rejected when the patient's immunosuppressive drugs were discontinued. The second patient had undergone a spontaneous regression of biopsy-proven metastatic stomach cancer 12 years before I first encountered him. Both cases suggested that the body's natural defenses could cause cancer regression in special cases.

When I came to the NIH in 1974, I began attempts to reproduce this phenomenon in other patients. My hypothesis was that the transfer to cancer patients of immune cells with anticancer activity could cause cancer regression and I began attempts to identify lymphocytes reactive against cancer antigens that we could use for adoptivetransfer. Substantial laboratory and animal experiments preceded our first human trials. We first immunized pigs with human tumors and transferred these immune pig lymphocytes to six patients with advanced cancer and saw no beneficial effects. The description of interleukin-2 (IL-2) in 1976 by R.C. Gallo and coworkers[1] at the NCI provided a great impetus to our work because IL-2 allowed us to grow T lymphocytes in vitro for the first time. These studies led us to the description of lymphokine-activated killer (LAK) cells in both mice and humans[2,3] which could distinguish fresh cancer cells from normal cells. Our paper in 1982 characterizing human LAK cells was also a *Citation Classic*®.[4] We successfully treated our first animals with established lung metastases using the combination of LAK cells and IL-2 in 1983.[56]

We then began Phase I clinical trials in patients with advanced cancer, first treating 39 patients with high-dose IL-2 alone and 27 patients with killer cells alone without seeing any anticancer responses. It was only when we combined LAK cells and IL-2 in late 1984 that we saw the first cancer regressions in humans with this immunotherapy approach. The first response occurred in a 33-year-old woman with metastatic melanoma who had tailed multiple attempts at surgical resection and treatment with interferon. Her cancers disappeared completely and she remains disease free now, ight years later.

In this paper we published our findings of the first 25 patients treated with the combination of LAK cells and IL-2. This work seemed to provide a major stimulus to studies of tumor immunology and experimental and clinical tumor immunotherapy and led to a resurgence of interest in the use of lymphokines and immune cells for cancer treatment. Wesubsequently showed that high dose IL-2 alone could also mediate anticancer effects and many other groups have now confirmed these findings. The development and current status of this work was summarized in the Karnofsky Lecture that I gave to the American Society of Clinical Oncology in 1991.[7]

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3. **Lotze M T. Line B R, Mathisen D J & Rosenberg** S **A.** The in vivo distribution of autologous human and murine lymphoid cells grown in T cell growth factor (TCGF): implications for the adoptive immunotherapy of tumors. *J. Immunol.* 125:1487-93. 1980. (Cued 165 limes)
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