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CCR 20th Anniversary Commentary: Autologous T Cells—The Ultimate Personalized Drug for the Immunotherapy of Human Cancer

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Summary

The article by Rosenberg and colleagues, which was published in the July 1, 2011, issue of *Clinical Cancer Research*, demonstrated the power of the adoptive transfer of autologous antitumor T cells to mediate the complete, durable, and likely curative regression of cancer in patients with heavily pretreated metastatic melanoma. It also provided a stimulus to the development of cell transfer approaches for other cancer types using both natural and genetically engineered lymphocytes.

Our paper, published in 2011, demonstrated that patients with metastatic melanoma treated with autologous anti-tumor T cells expanded in vitro could experience complete, durable and likely curative cancer regressions (1). In three consecutive clinical trials evaluating different lymphopreparative regimens that preceded the cell infusion plus interleukin-2 (IL-2) we reported objective responses by RECIST criteria in 52 of 93 patients (56%) including 20 patients (22%) with complete cancer regressions, 19 of whom had on-going complete responses beyond 3 to 5 years at the time of publication. Now, 4 years later, all of the 19 patients in complete response have on-going complete regressions from 63 to 137 months (median potential follow up of 9.8 years) and many are likely cured. These long-term results established the cellular basis of cancer immunotherapy in humans and helped explain the results of early trials with interleukin-2 (Il-2) alone, which resulted in a 6-7% incidence of complete regressions, the majority of which have been sustained up to 30 years after therapy (2, 3).

The role of lymphocytes in immune reactions became apparent only in the latter half of the 20th century. In 1958 the word lymphocyte was not listed in the index of The Journal of Immunology. In the early 1960s it became clear that cellular immune responses were involved in mediating allograft rejection as well as the protection of mice against the growth of transplanted tumors. Attempts at cancer immunotherapy in the human based on cellular immune reactions languished, however, and by the middle of 1970s, there was no clear evidence of an immune response against human cancer and no suggestion of the effectiveness of any human cancer immunotherapy.

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The description of T cell growth factor, later called interleukin-2 (IL-2), in 1976, the cloning of the gene encoding IL-2 in 1983, and the characterization of recombinant IL-2 in 1984 provided a means to simulate T cells in vivo (reviewed in ref. 4). In selected animal models the administration of high dose IL-2 could mediate regression of established tumor and these studies culminated in a report in 1985 that the administration of IL-2 to humans could mediate objective regressions in patients with metastatic cancer (2). A multi-institutional study confirmed that IL-2 administration could mediate objective responses in about 15% of patients with metastatic melanoma and metastatic renal cancer and that approximately 7% of these responses were complete, most of which were durable (5). These results led to the approval of IL-2 by the FDA for the treatment of metastatic renal cancer in 1992 and melanoma in 1998.

The definitive evidence that T lymphocytes were the mediators of these IL-2 induced anti-tumor responses came from our studies published in 1988 showing that tumor infiltrating lymphocytes (TIL) from solid human melanoma deposits could be expanded in vitro and when adoptively transferred in conjunction with IL-2 could mediate objective cancer regressions in patients with metastatic melanoma, including patients refractory to prior IL-2 administration (6). These results, were corroborated by the anti-tumor effects of TIL administration in mouse tumor models (7) and provided the first direct evidence that human T cells could mediate the rejection of human cancer and provided a stimulus to the study of T cell based immunotherapies in humans. These TIL also provided the necessary reagents to isolate the human tumor antigens recognized by these T cells and by the end of the 1990s multiple shared as well as unique tumor antigens were identified on human melanomas (reviewed in ref. 8).

Animal models of adoptive T cell transfer suggested that profound lymphodepletion of the host prior to T cell transfer could enhance the anti-tumor activity of the transferred cells. In 2002, we showed that this was the case in humans as well (9). Prior lymphodepletion increased the incidence of cancer regression in patients with metastatic melanoma and could result in the clonal repopulation of the transferred anti-tumor T cells in vivo. The improved results seen with lymphodepletion prior to cell transfer was due to multiple factors including the elimination of regulatory T cells and the elimination of endogenous lymphocytes that competed with the transferred cells for endogenous homeostatic cytokines such as IL-7 and IL-15, which showed increased levels in the lymphodepleted state. The increased stimulation of antigen presenting cells by toll-like receptors, likely from translocated bacteria in the presence of the induced neutropenia, also appeared to play a role (reviewed in ref. 10). Lymphocytes in a less differentiated state were more effective in mouse models and this was corroborated in the human by our studies showing that objective cancer responses were related to the administration of cells with shorter telomeres as well as cells that exhibited the early differentiation marker, CD-27 (1).

Our paper in 2011 consolidated these findings and showed that over half of patients with melanoma experienced objective responses to therapy with their autologous T cells plus IL-2 following a lymphodepleting regimen (1). Interestingly, in this study, as well as those repeated by others and our own recent study of 101 patients confirming these early results, we found that the likelihood of having a complete regression was unrelated to the site or

volume of metastatic cancer and was unrelated to any prior treatment that the patient had received including IL-2, chemotherapy, interferon or the anti-CTLA-4 checkpoint modulator, ipilimumab (1, 11, 12).

These studies raised the possibility that T cell transfer could be used to treat multiple cancer types though, until recently, it was extremely difficult, and often not possible, to identify T cells with reactivity against cancers other than melanoma. Genomic studies of melanoma TIL showed that T cells that mediated complete tumor regression recognized unique somatic mutations expressed by the cancer and that reactivity against these unique mutations elicited more effective anti-tumor responses than the melanoma/melanocyte differentiation antigens such as MART-1 and gp100 that had been the major focus of attention of immunologists (13, 14). These latter findings were in concert with the demonstration that cutaneous melanomas tended to accumulate more mutations than other solid cancers with the exception of smoking induced lung cancer and colon cancers with mismatch repair gene mutations. These strong correlations led to the possibility that immunologic reactivity against unique somatic mutations in common epithelial cancers might also be useful targets for cancer immunotherapy.

Recent studies using deep exomic sequencing of tumors in conjunction with high-throughput immunologic assessment have demonstrated the presence of autologous T cells that recognize epitopes encoded by somatic mutation on many common epithelial cancers. These findings led to the first successful treatment of a patient with a bile duct cancer treated with her own autologous T cells that recognized a unique ERBB2IP mutation expressed by her tumor (15). Following administration of these specific anti-tumor cells, the patient exhibited a near complete cancer regression of lung and liver metastases now ongoing beyond 2 years. In addition, transduction into normal lymphocytes of genes that encoded the TCR that recognized the ERBB2IP somatic mutation conferred anti-tumor reactivity to the normal cell which opened the possibility of introducing mutation-reactive TCRs into naive or central memory cells that will be highly proliferative when transferred to the host. Common epithelial cancers result in approximately 90% of all cancer deaths and the use of T cells or TCRs that recognize somatic mutations represents a path towards immunotherapy of these common cancers

Armed with evidence that T cell transfer could mediate cancer regression in vivo led to attempts to genetically modify normal lymphocytes with receptors reactive against tumor antigens. The first successful examples of the ability of genetically modified lymphocytes to mediate tumor regression in humans utilized T cell receptors against the MART-1 and gp100 shared melanoma/melanocyte differentiation antigens and although modest and incomplete cancer regressions were seen, toxicity to normal melanocytes in the eye and ear limited the application of this approach (16). These studies were extended to show that the treatment of patients with metastatic synovial cell sarcomas treated with T cells genetically engineered to express TCRs against the NYESO-1 cancer testes antigen could mediate cancer regression (17). T cells genetically engineered to express chimeric antigen receptors (CARs) against the CD-19 B cell antigen were shown to mediate complete regressions in patients with acute and chronic lymphocytic leukemia, follicular lymphomas, and aggressive diffuse large B cell lymphomas ((18) reviewed in (19)).

The use of a patient's own T cells that recognize a mutated antigen unique to that patient's cancer is a highly personalized cancer treatment. A new drug is created for each patient and, until very recently, this discouraged pharmaceutical companies from embracing the commercial application of this approach. Typically, pharmaceutical companies are devoted to the development of drugs in a vial that can easily be transported around the world. Investments of hundreds of millions of dollars in developing the first vial of a new drug are justified by the ability to produce the second vial at minimal cost. In adoptive cell transfer immunotherapy, however, a new drug must be created for every patient and thus, the current paradigm controlling drug development requires some modification. In the last few years multiple biotechnology companies have embraced the challenge of developing cell transfer therapies using autologous cells retrovirally transduced to express anti-CD-19 chimeric antigen receptors for the treatment of hematologic malignancies. In its current iteration, tumor or peripheral blood lymphocytes are shipped to a central facility where the anti-tumor T cells are generated and the cells returned to the original institution for infusion into the patient. Although this approach will be applicable for the small number of patients for whom shared tumor targets exist, the ability to apply recent advances targeting somatic mutations unique to each patient is another level of complexity confronting the commercial application of cell transfer therapy. The overwhelming majority of patients who develop metastatic disease from common epithelial cancers will die of those cancers despite the application of all currently available systemic modalities. This argues strongly for the vigorous development of highly personalized immunotherapy approaches in which the patient's own lymphocytes can be used to target mutations uniquely present on their cancer.

Cancer immunotherapy is in an exciting phase of its development. Our paper in 2011 demonstrated that T cell administration can lead to durable complete regressions in cancer patients. This approach as well as the ability to partially unleash the power of T cells by blocking checkpoint modulators has opened important new possibilities for the immunotherapy of human cancer.

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