

CCR Translations

Commentary on Cruz et al., p. 7058

MAGE: The Spell Is Broken

Katayoun Rezvani

The success of immunotherapy in Hodgkin lymphoma is hampered partly by limited expression of tumor-specific antigens in the malignant cells. One strategy to increase tumor immunogenicity may be to enhance the expression of Hodgkin lymphoma-specific antigens such as MAGE-A4 using epigenetic-modifying drugs in combination with cancer testis antigen-specific immunotherapy. *Clin Cancer Res*; 17(22); 6955–7. ©2011 AACR.

In this issue of *Clinical Cancer Research*, Cruz and colleagues (1) use an elegant approach to study the efficacy of epigenetic-modifying drugs in combination with cancer testis antigen (CTA)-specific immunotherapy in relapsed Hodgkin lymphoma. The authors successfully expanded T cells directed against the Hodgkin lymphoma-associated CTA MAGE-4 and showed that the epigenetic-modifying drug decitabine enhances the expression of MAGE-A4 in malignant cells and broadens MAGE-A4-specific immune responses *in vivo*.

Although most patients with Hodgkin lymphoma can be cured with conventional therapies, such as chemotherapy or radiotherapy, up to 30% of patients with advanced Hodgkin lymphoma will progress or relapse. More than half of relapsed and refractory patients will fail to respond to conventional salvage strategies, and the outlook for this subset of patients remains disappointing (2). Hodgkin lymphoma appears to be very susceptible to the allogeneic T-cell response that mediates the graft-versus-leukemia effect. Patients with Hodgkin lymphoma who relapse after allogeneic stem cell transplantation may achieve durable remission following donor lymphocyte infusion, showing the potency of donor-derived immunity in eradicating tumors (3). However, graft-versus-leukemia may be associated with more generalized donor T-cell alloreactivity, causing considerable morbidity and mortality from graft-versus-host disease. Furthermore, a substantial number of relapsed Hodgkin lymphoma patients may not be eligible for allogeneic stem cell transplantation due to the lack of a donor or poor general fitness for this treatment. Thus, there is an urgent need to develop effective and nontoxic therapeutic approaches for this group of poor-risk patients.

One potential option lies in immune therapies that target tumor-specific antigens.

Approximately one third of cases of Hodgkin lymphoma in the Western world are associated with the expression of Epstein-Barr virus (EBV)-derived antigens in malignant Reed-Sternberg cells, making this tumor a potential target for EBV-targeted immunotherapy (4). Bollard and colleagues pioneered T-cell immunotherapy against EBV for Hodgkin lymphoma. In elegant proof-of-principle studies (5, 6), they showed the feasibility of generating autologous patient-derived polyclonal EBV-specific T cells, and they confirmed the *in vivo* persistence and antitumor activity of such cells following adoptive transfer in patients with refractory Hodgkin lymphoma.

However, the malignant cells in EBV-positive Hodgkin lymphoma express only a limited number of EBV-derived antigens that are poorly immunogenic, such as EBV nuclear antigen 1 and latent membrane proteins 1 and 2 (7). Furthermore, this therapy is only applicable to the subset of patients with EBV-positive disease. CTAs offer an attractive alternative target for immunotherapy due to their highly restricted expression in normal human tissues and strong natural immunogenicity (8). MAGE-A4 is a Hodgkin lymphoma-associated CTA that is expressed by a subset of patients with EBV-negative Hodgkin lymphoma, and its expression can be enhanced by the demethylating agent decitabine (9, 10).

Using an overlapping peptide library spanning the MAGE-A4 protein, Cruz and colleagues (1) successfully expanded MAGE-A4-specific T cells from healthy donors as well as a number of patients with relapsed Hodgkin lymphoma. The use of overlapping synthetic peptides rather than a single epitope for the generation of T-cell lines has a number of potential advantages. The generation of broader immune responses to multiple epitopes from MAGE-A4 overcomes the need to identify target antigens in the context of an HLA allele and reduces the risk of epitope escape mutants. Furthermore, the provision of CD4⁺ T-cell help as well as CD8⁺ T cells will ensure the *in vivo* expansion, persistence, and optimal antitumor activity of the MAGE-A4-specific T-cell population following adoptive transfer (11). The observation that MAGE-A4-

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specific T cells can be successfully generated from patients with Hodgkin lymphoma even after salvage high-dose chemotherapy further supports the feasibility of developing clinical protocols for adoptive immunotherapy with *ex vivo*-expanded MAGE-A4-specific T cells in this group of patients in the autologous setting.

Convincing data suggest that demethylating agents such as decitabine enhance the expression of epigenetically repressed CTA in solid tumors and hematologic malignancies, thereby potentially increasing tumor immunogenicity. Furthermore, the effect of DNA-demethylating agents on CTA gene expression appears to be selective, with preferential upregulation in cancer cells but not in normal epithelia or lymphoid cells (12). This difference may be due in part to differences in the methylation status and proliferation rates of these cells. The selective upregulation of CTA on cancer cells should allow their selective recognition by CTA-specific T cells with minimal risk of inducing autoimmunity.

In their study, Cruz and colleagues (1) sought to examine the feasibility of modulating methylation with decitabine as a strategy to enhance T-cell responses against MAGE-A4. The authors report that upregulation of MAGE-A4 expression by decitabine resulted in increased recognition of Hodgkin lymphoma cell lines by cytotoxic T lymphocytes. Intriguingly, the authors show that treatment with a decitabine-

containing regimen resulted in the induction of a broader MAGE-A4-specific T-cell response in patients with Hodgkin lymphoma. This observation suggests that upregulation of MAGE-A4 following treatment with decitabine results in the development of epitope spreading, with recruitment of a diversified repertoire of T cells that may also react to subdominant and/or cryptic tumor-derived epitopes. The phenomenon of epitope spreading has long been known to play a role in the pathogenesis of autoimmune conditions. Epitope spreading also appears to play an important role in tumor immune responses in patients with cancer, and it has been shown to be associated with improved outcome following vaccination (13). It is therefore possible that one of the mechanisms by which demethylating agents such as decitabine may exert an antitumor effect is through the induction or amplification of a host T-cell immune response to upregulated tumor antigens.

In conclusion, the observation that demethylating agents may modulate a tumor-specific immune response suggests that epigenetic therapies might be used to enhance the clinical activity of immunotherapeutic strategies. The collected findings by Cruz and colleagues (1) strongly support the rationale for combining epigenetic agents with CTA-specific immunotherapy. A combination regimen of a demethylating agent such as decitabine together with

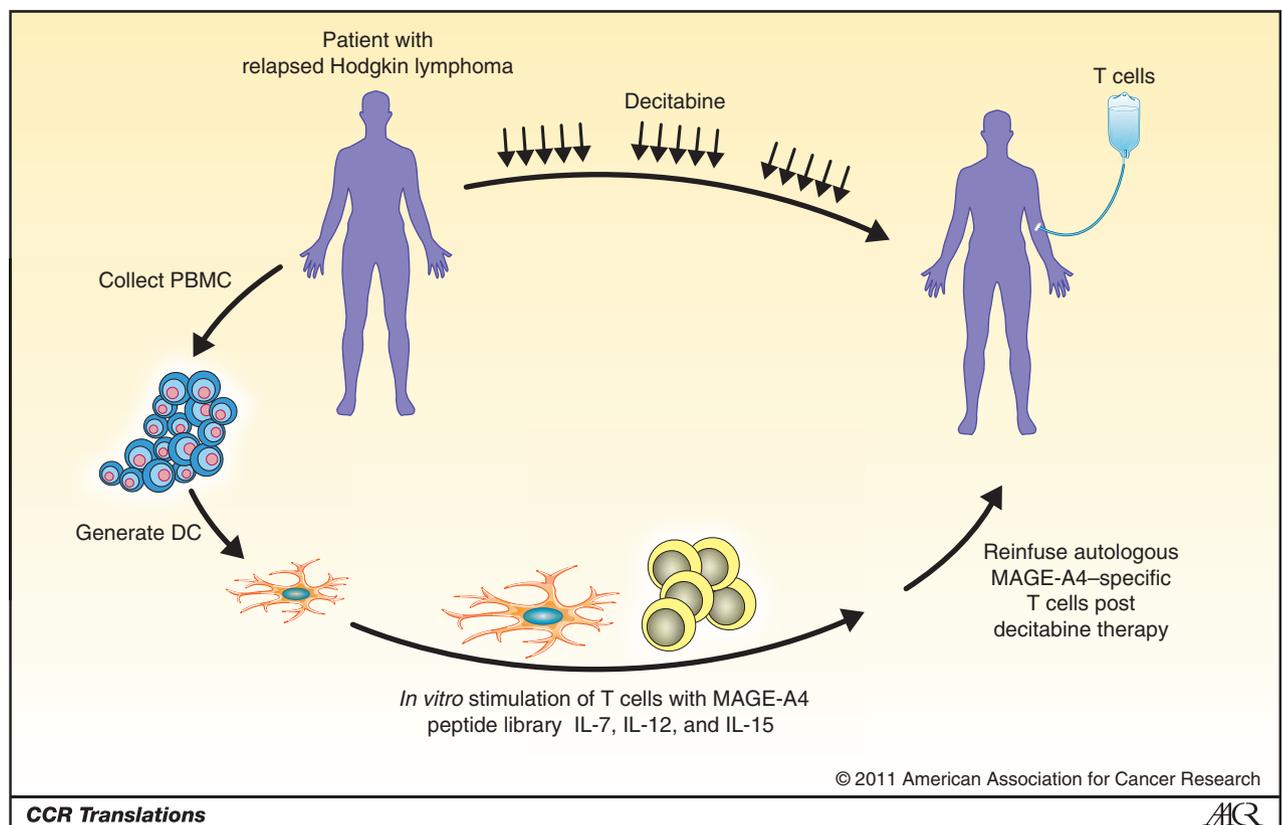


Figure 1. Proposed strategy for a clinical trial using decitabine together with adoptive transfer of *ex vivo*-generated MAGE-A4-specific T cells in patients with relapsed or refractory Hodgkin lymphoma. DC, dendritic cell; IL, interleukin; PBMC, peripheral blood mononuclear cell.

adoptive transfer of *ex vivo*-generated MAGE-A4-specific T cells in patients with relapsed or refractory Hodgkin lymphoma could be incorporated into a first clinical trial to test the hypothesis that CTA-specific immunotherapy has therapeutic benefit in cancer (Fig. 1).

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