

# Adoptive T cell therapy: Back to the future

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## Abstract

The use of antigen-specific T cells for adoptive therapy offers an opportunity to dissect the requirements for effective immunotherapy. We postulate that basic principles established from murine studies of adoptive immunotherapy performed decades ago may be operative in human clinical trials. We examine the use of CD4 helper T cells as a means to augment *in vivo* persistence and the use of pre-infusion lymphodepletion to condition patients prior to adoptive transfer.

accompanied in some cases by complete and partial responses in patients with refractory metastatic melanoma.

## Adoptive CD4 T cell therapy

The class II-restricted epitopes for tyrosinase and NY-ESO-1 were used to generate antigen-specific CD4 T cell clones from the peripheral blood of patients with metastatic melanoma. All patients had progressive disease refractory to conventional therapy and tumor expressing the targeted antigen. Among 9 patients treated in a dose escalation study of a single infusion of antigen-specific CD4 T cells at cell doses of  $10^9$ ,  $3.3 \times 10^9$  and  $10^{10} / m^2$ , one complete, and a total of three mixed, partial and stable responses were observed; in two patients failing at lower dose levels, clinical responses were observed when re-treated with higher doses of CD4 T cells suggesting a dose-response effect. For some patients, we observed the development of endogenous CD4 and CD8 T cell responses to non-targeted melanoma-associated antigens. Tumors from these patients expressed absent to low levels of Class II, suggesting that localized recruitment of non-specific effectors by infused antigen-specific CD4 T cells may have led to tumor killing that was augmented by the expansion of endogenous tumor-associated antigen-specific T cells through cross-presentation. Infused antigen-specific CD4 T cells may have additionally contributed by 'licensing' dendritic cells and engendering a pro-inflammatory milieu.

To more directly assess the contribution and efficacy of CD4 T cells to the CD8 T cell response, a study using adoptively transferred CD8 T cells in the absence or presence of co-administered CD4 T cells is currently underway.

## Adoptive therapy following lymphodepletion

Strategies to deplete regulatory cells and/or enhance homeostatic mechanisms to augment *in vivo* persistence and function were applied in clinical trials of adoptive therapy using first, fludarabine, and subsequently, high-dose cyclophosphamide. While fludarabine lymphodepletion led to elevated levels of serum IL-7 and IL-15 and an *increase* in persistence of transferred T cells of nearly 3-fold (up to 21 days), recovery from lymphodepletion led to an increase in the regulatory : effector T cell ratio and only modest clinical responses.

The use of high-dose cyclophosphamide preceding adoptive transfer of antigen-specific CD8 T cell clones followed by low dose IL-2 ( $250,000 U/m^2$ ) appears in early studies to provide an extended duration of *in vivo* persistence (more than 300 days)