

# Generating therapeutic/protective T-cell responses to tumors and HIV: "More is better, but will it be enough?"

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## Abstract

T cells can mediate potent responses to tumors and viruses, providing protection from the development of disease and eradicating existing disease. However, tumors and viruses can evade T-cell responses by multiple mechanisms, and generating effective T-cell responses will require designing strategies that overcome or circumvent these obstacles.

T cells targeting established tumors and chronic infections, if not immediately effective, are confronted by the obstacle of persistent stimulation by antigen, an event that commonly leads to reduction of effector activity and ultimately tolerance or deletion. Insights into the mechanisms by which potentially reactive T cells are rendered unresponsive, and strategies that may overcome such loss of activity, will be discussed.

Therapeutic vaccination in patients with existing tumors or HIV infection provides an opportunity to expand the frequency of reactive T cells in the host, and is based on the presumption that such responses can eliminate the tumor/virus. To better understand the requirements for success and/or reasons for failure, we have examined adoptive T-cell therapy with *in vitro* expanded tumor- or HIV-specific T-cell clones of defined function and avidity as a model for what can be achieved by vaccination. Preliminary studies in patients with relapsed leukemia and established HIV infection on HAART therapy will be presented.

Many parameters impact the efficacy of a vaccine, such as the ability to induce responses of appropriate magnitude and function that can persist and localize to the required site *in vivo* where effector activity is required. Developing such vaccines would benefit from the availability of murine models that better mimic human responses and permit efficient analysis of the responses elicited and the limitations and advantages of individual vaccine vectors. Efforts to develop the requisite genetically-modified mice, including the replacement of selected murine genes with human genes, and to establish informative murine models will be discussed, particularly in the context of the current HIV vaccine effort, but the results should also have implications for tumor vaccines.