Overcoming barriers to programming a therapeutic cellular immune response to fight melanoma

David Baltimore[1], Owen N. Witte[2,3,4], Lili Yang[1], James Economou[2,5] and Antoni Ribas[3,6,7]

[1]Division of Biology, California Institute of Technology, Pasadena, CA, USA
[2]Department of Microbiology, Immunology and Molecular Genetics, University of California Los Angeles (UCLA), Los Angeles, CA, USA
[3]Broad Stem Cell Research Center (BSCRC), UCLA, Los Angeles, CA, USA
[4]Howard Hughes Medical Institute at UCLA, Los Angeles, CA, USA
[5]Departments of Surgery and Molecular and Medical Pharmacology, UCLA, Los Angeles, CA, USA
[6]Division of Hematology-Oncology, Department of Medicine, UCLA, Los Angeles, CA, USA
[7]Jonsson Comprehensive Cancer Center (JCCC), UCLA, Los Angeles, CA, USA
Correspondence David Baltimore, e-mail: baltimo@caltech.edu

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Dear Sir,

Metastatic melanoma can undergo sustained remissions when a T cell mediated cellular immune response is activated by vaccination strategies, immune stimulating cytokines such as interleukin-2 (IL-2), or immune modulating monoclonal antibodies such as blocking antibodies to cytotoxic T lymphocyte-associated antigen 4 (CTLA4) (Ribas, 2006). Although response rates are low, the patients with a response can have long term benefit. These strategies rely on the ability to expand an endogenous T cell response to cancer, and limiting numbers of T cells with cancer-specific T cell receptors (TCRs) may be a major reason for the low response rates. This limitation can be overcome with adoptive cell transfer (ACT) strategies, where large numbers of cancer-specific cytotoxic T lymphocytes (CTLs) are administered to patients.

Attempts have been made to generate large pools of tumor antigen-specific lymphocytes for ACT from autologous tumor-infiltrating lymphocytes (TILs) expanded from tumor biopsies (Rosenberg et al., 2008), or by cellular cloning of antigen-specific lymphocytes expanded from peripheral blood mononuclear cells (PBMC) upon repeated antigen exposure (Yee and Greenberg, 2002). We showed, in mice, that genetic engineering of hematopoietic stem cells (HSC) with TCRs can continuously generate tumor antigen-specific CTL (Yang and Baltimore, 2005; Yang et al., 2002). In preparation for applying this concept to humans, we have initiated a program of clinical trials, beginning with TCR engineering of peripheral T cells in melanoma patients. This follows the demonstration that PBMC can be genetically redirected to become tumor-specific using viral vector-mediated transduction of TCR chains (Johnson et al., 2009; Morgan et al., 2006; Schumacher, 2002).

To improve the effectiveness of the procedure we have both limited the in vitro expansion of the engineered T cells and have added a peptide-pulsed in vivo dendritic cell stimulation to the protocol. We have now treated five patients with TCR-modified cells and have seen that the procedure is well tolerated and have found by PET scanning that some of the patients show a dramatic reduction in metastatic lesions. We are continuing this program with more patients, continuing close surveillance of the treated patients and planning modifications of the therapy, leading to treatment with modified stem cells.

This work is a collaborative effort of basic science laboratories at Caltech and more clinically oriented scientists at UCLA. It is an example of what can be accomplished by a collaborative, interdisciplinary approach. Translational science requires large teams that span the landscape from model systems to clinical application. We have chosen to focus on melanoma because it is particularly tractable for an immunotherapeutic approach. However, it is our hope and belief that the principles that can be established in melanoma treatment will have wider application in cancer and we have begun to extend our purview to other malignancies.

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