

# Checkpoint blockade in tumor therapy: New insights and opportunities

James P. Allison

*Ludwig Center for Cancer Immunotherapy, Howard Hughes Medical Institute Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

## Abstract

Over the past several years it has become apparent that the effectiveness of active immunologic strategies for cancer therapy have been limited by cell intrinsic and extrinsic regulatory pathways that act in concert to shape the magnitude, quality, and location of immune responses in order to maximize target destruction and minimize harm to normal tissues. The prototype of cell intrinsic "checkpoints" whose blockade enhances anti-tumor responses is CTLA-4, which has been extensively studied in a large number of animal models and shown to be quite effective in achieving, either as a single agent or in combination with other agents, complete tumor eradication and long lasting tumor immunity. Over 3,500 patients have been treated with an antibody to human CTLA-4 (Ipilimumab, Medarex and Bristol-Meyers Squibb). Significant responses, including complete remissions, have been observed in about 15% of metastatic melanoma patients. This has led to considerable effort to identify biomarkers that would be useful in determining the impact of CTLA-4 on human immune responses in order to identify changes that might correlate with clinical responses, as well as to address combinatorial strategies that might enhance the effectiveness/frequency of clinical responses.

We have shown in melanoma and prostate cancer models in mice that tumor rejection is closely correlated with an increase in the ratio of both CD4 and CD8 effector cells to FoxP3+ regulatory cells. We have also found that CTLA-4 blockade decreases either the conversion of self reactive FOXP3- effector CD4 T cells to Foxp3+ Treg and/or the migration of converted cells into the tumor.

In a presurgical bladder cancer trial it has been shown that CTLA-4 results in an increase in the ratio of IFN- $\gamma$  producing effector cells that express high levels of the CD28/CTLA-4 homolog ICOS. We have confirmed this in mouse models of melanoma and prostate cancer, and preliminary data suggest that an antibody to ICOS can enhance the therapeutic effects of anti-CTLA-4 in a melanoma model. We have also shown that intratumoral T cells express high levels of another coinhibitory molecule, PD-1, in which there has been considerable interest recently, and have found that blockade of PD-1 together with CTLA-4 enhances anti-tumor responses.

We have also examined two new combinatorial therapies involving CTLA-4 blockade: cryoablation and adoptive T cell transfer. In both we found significant synergy resulting in rejection of tumors that either treatment alone could not achieve.