



## Combination immunotherapy for cancer



Insight from  
Douglas Fearon

In this issue, Chapuis et al. describe the response of a single patient with metastatic melanoma to combination immunotherapy with anti-CTLA4 and adoptive T cell therapy (1). Although *JEM* usually discourages the submission of single case studies, the editors, like the authors, realized that this patient was unusual. He had previously been treated with anti-CTLA4 and adoptive T cell therapy administered as monotherapies, with only possible slowing of tumor growth with the former, and no response to the latter. The subsequent complete and durable clinical response to simultaneous treatment with these two modalities, therefore, allowed an argument to be made that their combination was responsible for the improved outcome.

The efficacy of blocking antibodies to CTLA4, PD1, PD-L1, and adoptive T cell therapy, including CAR T cells, has been established, but only a minority of patients with certain cancers respond. The challenge now is to increase both the proportion of patients and the types of cancers that respond to immunological interventions. The finding by Chapuis et al., when taken together with an earlier demonstration of the clinical benefit of combining anti-CTLA4 and anti-PD1 in patients with melanoma (2), argues that combining interventions that target different components of an anticancer immune response may be a feasible strategy. The question is, how will the most therapeutically effective combinations be determined?

Chapuis et al. combined adoptive T cell therapy with anti-CTLA4 because “an ex vivo source of melanoma-reactive CTL might not only provide sufficient substrate for anti-CTLA4 to enhance tumor lysis, but also trigger the development of de novo responses to nontargeted antigens.” Postow et al. (2) combined anti-CTLA4 and anti-PD1 because “in preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.” These clinical experiments were based on preclinical experimental work, as is appropriate. How might this rationally scientific pathway be enhanced?

The Chapuis et al. study also addresses this issue. Instead of being funded by the pharmaceutical industry, financial support was derived from the government and SU2C, a charitable program of the Entertainment Industry Foundation. This may become the model for cancer immunotherapy. There has been remarkable philanthropic support for this field, as exemplified not only by SU2C, but also by the recent gifts from Michael Bloomberg, Sidney Kimmel, and Sean Parker to establish cancer immunology centers at several academic institutions. This development will allow clinical investigators to focus only on science when developing strategies for combination immunotherapies.

1. Chapuis, A.G., et al. 2016. *J. Exp. Med.* <http://dx.doi.org/10.1084/jem.20152021>

2. Postow, M.A., et al. 2015. *N. Engl. J. Med.* 372:2006–2017.

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