Published OnlineFirst January 9, 2014; DOI: 10.1158/0008-5472.CAN-13-2216

Letter to the Editor

Cancer Research

Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors—Letter

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There is much effort to develop new therapeutic approaches to rescue dysfunctional T cells in patients with cancer. In the June issue of *Cancer Research*, Duraiswamy and colleagues demonstrate that a triple therapy consisting of anti-PD-1, anti-CTLA-4, and therapeutic vaccination provides consistent rejection of experimental tumors (1). This triple therapy was better than any single- or double-agent combination.

The study by Duraiswamy and colleagues has much translational relevance (1) as new clinical data demonstrate that antagonistic antibodies blocking PD-1 and/or CTLA-4 provide strong responses to some but not all patients (2–4). Interestingly, the limited objective response rate seems to also apply to patients with a presumed preexisting tumor-reactive T-cell response (3, 5). Therefore, the importance of the Duraiswamy study is that it identified an approach that may extend objective response rates to a greater percentage of patients.

The study treated mice 3 or 10 days after inoculation of murine colon or murine ovarian cancer cells, respectively (1). At that time, mice still lacked or had barely detectible tumor nodules. However, it takes approximately 14 days and a tumor burden for initially functional tumor-reactive T cells—generated in response to cancer cell inoculation—to become dysfunctional (6, 7). Therefore, it would be important to know whether the approach described by Duraiswamy and colleagues prevented the development of T-cell dysfunction or rescued existent T-cell dysfunction, and how anti-CTLA-4 and PD-1 blockade contributed to the rescue if observed. Using at least 14-day-old tumors exceeding 100 mm^3, we found that vaccination with antigen-producing bacteria combined with PD-1 blockade eradicated tumors, but combining anti-CTLA-4 with PD-1 blockade did not improve outcomes (7).

Some vaccines may be effective in preventing but not rescuing T-cell dysfunction (8), and preventative approaches may not be effective in treating patients already in a state of T-cell dysfunction. Thus, it would be important to extend experimental studies by Duraiswamy and colleagues by testing the capacity of different types of vaccines and immunoinhibitory pathway blockades to rescue endogenous T cells in unmanipulated long-established experimental tumors.

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doi: 10.1158/0008-5472.CAN-13-2216

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This research was supported by the NIH grants P01-CA97296, R01-CA22677, and R01-CA37516 to H. Schreiber and the Graduate Training in Growth and Development grant T32 HD009007 to D.C. Binder.

Received August 7, 2013; accepted August 16, 2013; published OnlineFirst January 9, 2014.

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Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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Cancer Res 2014;74:632. Published OnlineFirst January 9, 2014.