Nature Reviews Clinical Oncology published online 29 April 2014; doi:10.1038/nrclinonc.2013.208-c2

REPLY

Regulatory T cells—an important target for cancer immunotherapy

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We appreciate very much the correspondence from Shin & Ha regarding an important role for regulatory T cells (T_{REG}) in antitumour immunity (Regulatory T cells—an important target for cancer immunotherapy. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.208-c1),[1] and their suggestion that this topic was somewhat neglected in our recent Review on cancer immunotherapy (Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. *Nat. Rev. Clin. Oncol.* **11**, 24–37 [2014]).[2] In their thoughtful letter, they highlight several murine and human *in vitro* studies suggesting that manipulation of T_{REG} number and/or function may be an important consequence of immune checkpoint blockade. In that regard, we concur completely with their assessment that the effects of CTLA-4 blockade in regulating T_{REG} of patients with cancer remains unclear. Whereas two recent animal studies[3,4] showed that anti-CTLA-4 antibodies can deplete T_{REG} that express relatively high levels of CTLA-4, the clinical relevance of these data is slightly undermined by the clinical observation that polymorphisms of human Fc receptors (*FcRs*) did not seem to correlate with the efficacy of anti-CTLA-4 in a fairly large series of patients with melanoma; such a correlation might be expected if FcR-mediated T_{REG} depletion was the major mechanism by which this agent functions.[5] *In vitro* studies of human T cells treated with anti-PD-1 or anti-PD-L1 antibodies showed a decreased expression of FOXP3 in T_{REG};[6] however, to our knowledge these findings have not yet been replicated *in vivo* or in patients treated with monoclonal antibodies to PD-1 and/or PD-L1 in clinical trials. Perhaps the most important challenge in cancer immunotherapy involving T_{REG} manipulation is that there are still no extracellular molecules absolutely specific to T_{REG}; the vast majority of these molecules are, in fact, expressed on activated CD4 T cells as well. Furthermore, targeting T_{REG} with antibodies directed against C-C chemokine receptor type (CCR-4)[7] or even to lymphocyte activation gene 3 protein (LAG-3)[8] is a viable clinical strategy; however, these approaches are in a relatively earlier stage of development compared to the immune checkpoint and vaccine regimens discussed in our Review.

Nevertheless, we are in complete concurrence with Shin & Ha that a combined immunotherapy regimen—which includes specific targeting of T_{REG}—represents a promising strategy, particularly for either advanced-stage disease or for the many tumour types that have not shown objective responses to single-agent immune checkpoint blockade.

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Competing interests
C.G.D. has served as a paid consultant to BMS, CoStim Pharmaceuticals, Dendreon, Genentech–Roche, and Pfizer Inc. J.R.B. has served as an unpaid advisory board member to BMS and a paid consultant for Merck. E.J.L. declares no competing interests.

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