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REPLY

Low-dose IL-2 therapy — a complex scenario that remains to be further explored

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We thank Zhanguo Li, Jing He, and Di Yu for their correspondence (The rise of IL-2 therapy — a picture beyond T_{reg} cells. *Nat. Rev. Rheumatol.*; 2017)[1] about our commentary (Humrich, J. Y. & Riemekasten & G. The rise of IL-2 therapy — a novel biologic treatment for SLE. *Nat. Rev. Rheumatol.* **12**, 695–696; 2016)[2], which discussed their study of low-dose IL-2 therapy in systemic lupus erythematosus (SLE)[3].

We agree that low-dose IL-2 therapy exerts effects on other cell subsets apart from regulatory T (T_{reg}) cells and that the clinical efficacy of this treatment modality might not only be explained by the exclusive targeting of T_{reg} cells. Owing to its pleiotropy in general, IL-2, even when applied in low doses, indeed has some effects on other cells such as conventional $CD4^+$ T cells, natural killer cells and $CD8^+$ T cells (see also von Spee-Mayer *et al.*[4]).

He *et al.*[3] focused their investigations on effects of low-dose IL-2 therapy on T follicular helper (T_{FH}) and type 17 T helper (T_H17) cells, which of course is a sound rationale in light of their previous observations. In their study, He *et al.* defined T_{reg} cells based on protocols reported in 2006 (REFS 5,6). However, the appropriate application of these well-elaborated protocols depends on the research questions being explored, as these protocols were mainly developed to selectively enrich human T_{reg} cells for *in vitro* functional studies. The respective studies demonstrated that the inclusion of surface CD127 for T_{reg} cell analysis results in an improved flow-cytometry-based distinction between genuine T_{reg} cells and activated conventional T cells, which transiently express CD25 in particular, as well as FOXP3 (REFS 5,6). These analyses also included staining for FOXP3 and the authors did not suggest omitting FOXP3 in flow-cytometry-based T_{reg} cell analyses. One of the main messages of these works was that CD127, or the combination of CD127 and CD25, is better than CD25 alone for distinguishing between T_{reg} cells and activated conventional T cells, which is highly relevant for the 'live' isolation of T_{reg} cells for functional analyses and *in vitro* studies[5,6].

In our previous analyses[4], a small proportion of $FOXP3^+CD127^{lo}CD25^-$ T cells produced cytokines (~10–15% in patients with SLE) and we found that this cell subset was less demethylated in the T_{reg}-specific demethylated region compared with the $FOXP3^+CD127^{lo}CD25^+$ T_{reg} cell subset, indicating that some of these $FOXP3^+CD127^{lo}CD25^-$ T cells are indeed activated conventional T cells. However, and in contrast to cells from healthy individuals, the majority of these $FOXP3^+CD127^{lo}CD25^-$cells could still be considered *bona fide* T_{reg} cells in patients with SLE as they expressed high levels of surrogate markers for T_{reg} cells (such as Helios) and most did not express cytokines. In addition, these $FOXP3^+CD127^{lo}CD25^-$ cells could re-express the IL-2 receptor α-chain CD25 upon IL-2 exposure[4].

In any case, we thank our colleagues for their important contribution to this vibrant research field and we hope very much for our patients that this novel therapeutic concept will find its way into routine clinical practice regardless of its underlying mechanisms.

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Competing interests statement
The authors declare no competing interests.