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Regulatory T cells: recommendations to simplify the nomenclature

To the Editor:

Regulatory T cells (T_{reg} cells) have attracted much interest from both basic and clinical immunologists. Although questions remain about their fundamental biology and their clinical potential has yet to be fully realized, considerable advances have been made in the understanding of the differentiation, homeostasis and function of T_{reg} cells. This new knowledge has led to a substantial increase in the number of Foxp3$^+$ T_{reg} cell subpopulations described in the literature and consequently to an increase in the use of new abbreviations and terminology. Furthermore, as the understanding of T_{reg} cell biology has grown, so too has the realization that some aspects of the original terminology are no longer accurate, and its use has become less stringent. At the Third International Conference on Regulatory T Cells and Th Subsets and Clinical Application in Human Diseases held in Shanghai, China, on 13–16 October 2012, a small workshop was convened to discuss T_{reg} cell nomenclature and to develop several recommendations. We hasten to add that this is simply a list of recommendations, and it remains the prerogative of journals to develop their own editorial preferences and for the authors to use the nomenclature they feel best suits their manuscript. However, we support the recommendations noted below.

There were three general issues that provided the momentum for this workshop. First, the terms used for the principal Foxp3$^+$ T_{reg} cell populations—those that differentiate in the thymus, those that differentiate in the periphery and those generated *in vitro*—are not ideal, as these are, to some extent, inaccurate, ambiguous and/or uninformative. For example, the widely used term 'natural T_{reg} cell' is misleading and ambiguous, as it indicates that all other Foxp3$^+$ T_{reg} cell populations are 'unnatural'. It also does not convey any useful or accurate information. One feature of these Foxp3$^+$ T_{reg} cell populations that is more informative is the anatomical location of their differentiation. Instead, use of the terms 'thymus', 'periphery' and '*in vitro*' provides a clear indication of whence the Foxp3$^+$ T_{reg} cells in question are derived. Thus, we would recommend that 'natural Foxp3$^+$ T_{reg} cells' instead be referred to as 'thymus-derived T_{reg} cells' (**Box 1**). Consistent with the rationale above, we would recommend that Foxp3$^+$ T_{reg} cells that differentiate in the periphery be referred to as 'peripherally derived T_{reg} cells' rather than 'induced or adaptive T_{reg} cells' (**Box 1**). In this context, we noted that terms used to define a T_{reg} cell subpopulation, such as 'induced T_{reg} cells', are often used when the location of their differentiation is unclear. Thus, we would suggest that the newly recommended terms 'thymus-derived T_{reg} cells' and 'peripherally derived T_{reg} cells' be used only when the anatomical location of their differentiation has been clearly demonstrated. When the origin of the T_{reg} cell being studied is unclear, the general term 'Foxp3$^+$ T_{reg} cell' would be more appropriate. Finally, to clearly distinguish between Foxp3$^+$ T_{reg} cell populations that are generated *in vivo* versus those generated *in vitro*, we would suggest that the term '*in vitro*–induced T_{reg} cells' be used for all Foxp3$^+$ T_{reg} cell populations generated *ex vivo*, such as those generated through the use of transforming growth factor-β (**Box 1**).

Second, there has been a growing tendency to use terms such as 'T_{reg} cells' or 'iT_{reg} cells' when confirmation of such identity is lacking. The frequent use of the term 'T_{reg} cells' has been a particular problem in studies focusing on human T_{reg} cells, as activated conventional T cells can also express Foxp3. The term 'T_{reg} cell' should be used only when it is clear that the cells have (or had) suppressive ability or have a transcriptional, epigenetic and/or protein-expression signature that suggests that the cells in question are, beyond a reasonable doubt, Foxp3$^+$ T_{reg} cells (**Box 1**). Also, as indicated above, the terms 'thymus-derived T_{reg} cell' and 'peripherally derived T_{reg} cells' should be used only when the anatomical location of their development has been clearly demonstrated.

Third, there has been progressive growth in the development and use of new T_{reg} cell terminology that is likely to lead to more confusion and the further 'jargonization' of immunology. Until a new population has been extensively demonstrated to be unique, distinct from other populations and stable, we would recommend not coining new terms for such subpopulations (**Box 1**). Instead, we would encourage investigators to identify them through the use of prominent aspects of their expression pattern, such as a transcription factor or cytokine. Although the focus of this Correspondence has been CD4$^+$Foxp3$^+$ T_{reg} cell populations, many CD4$^-$Foxp3$^-$ T_{reg} cell populations have been described, and we would similarly recommend that new terms be used to describe these only when their identity and stability have been clearly defined.

Box 1 T_{reg} cell nomenclature recommendations

1. 'Thymus-derived T_{reg} cell (tT_{reg} cell)' should be used instead of 'natural T_{reg} cell (nT_{reg} cell)'.

2. 'Peripherally derived T_{reg} cell (pT_{reg} cell)' should be used instead of 'induced or adaptive T_{reg} cell (iT_{reg} cell or aT_{reg} cell)'.

3. '*In vitro*–induced T_{reg} cell (iT_{reg} cell)' should be used to clearly distinguish between those T_{reg} cell populations generated *in vivo* versus those generated *in vitro*.

4. T_{reg} cell terms should be used only when there is definitive evidence justifying their use.

5. The development and use of new T_{reg} cell terminology should be limited, especially for subpopulations.

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