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The break on immune tolerance is a common point between autoimmune diseases and the uncontrolled effector immune responses against allo-antigens in transplantation. Among the past years, several approaches to restore a suppressive immune state have included the targeting of co-stimulatory/inhibitory molecules on immune cells, the promotion or blockade of pivotal cytokines, and the extensive study on how to isolate and expand suppressive cells with the purpose to re-infuse them in patients. To date, the availability of new technologies has permitted to learn, in a more detailed way, the immune mechanisms carried out by suppressive lymphocytes, together with the identification of new potential candidates to target in our quest for immune tolerance. For example, the attractive concepts of lymphocyte plasticity and function stability, supported by the finding of new transcription factors, have opened a new window in the understanding of T cell differentiation, effector cell commitment and immune regulatory function. On the other hand, the discovery of new members of the Ig superfamily ligand, VISTA; the intriguing role of modulatory molecules like Retinoic Acid, Neuropilin-1, Fc gamma receptors, or cytokines such as IL-33, among others, are revealing new possibilities in the development of new strategies to conquer our obsession: immune tolerance. Here, we gather the latest information regarding new targets and cellular processes, including an update on current cellular therapies and the exciting coming approaches to cure

autoimmunity and permit transplant acceptance.