• Although Treg are essential for the prevention of autoimmune diseases, their immunoregulatory function may hinder the induction of immune responses against cancer and infectious agents.
• FOXP3 transcription factor is essential for the specification and maintenance of Treg cells, and thus, it is considered as the “master regulator” of Treg cells.
• Development of inhibitors of FOXP3 might give new therapeutic opportunities for these diseases.
• We identified a peptide (named P60) able to enter into the cells, bind to FOXP3, and impair Treg activity in vitro and in vivo (Patent ES2328776, WO2009065982).
• P60 binds to the intermediate region of FOXP3 and inhibits its homodimerization and interaction with the transcription factor AML1/Runx1.
• Characterization has been performed to identify those residues which contribute to the stability of P60-FOXP3 interactions. Combinatorial mutation analysis has allowed us to identify P60-derived peptides with higher Foxp3 binding affinity and stronger biological activity than the original P60.
• **Indication:** Cancer and Chronic viral infections.

**Approach**

There are no available compounds able to inhibit Treg activity. We found that P60 derived peptides are able to inhibit Foxp3 dimerization and its interaction with AML1/Runx1 transcription factor. P60 derived peptides impair the immunosuppressive activity of Tregs and constitute a strategy to enhance antitumor and antiviral immunotherapies.

**Key concepts and Target Identification**

• Dimerization of FOXP3 is required for its function as a transcriptional regulator and it has been described that the leucine zipper region is necessary and sufficient to mediate homo-dimerization
• AML1 is required for IL-2 and IFN-γ gene expression in conventional CD4+ T cells and its interaction with Foxp3 is needed for the immunosuppressive activity of Tregs
• Activation of naïve T-cells through TCR cross linking can activate a transient FOXP3 expression which is strongly associated with hypo responsiveness of T-cells.
• P60 derived peptides inhibit FOXP3 homodimerization and FOXP3/AML1 interaction impairing the immuno-suppressive activity of Treg cells and enhancing T cell proliferation and cytokine production upon TCR stimulation.
• P60/P60 derived peptides are identified as regulators of Treg and as potential agents for tumor immunotherapy.

**Target Validation**

- Treg inhibitory peptide P60 interacts with the intermediate region of FOXP3 inhibiting homodimerization and its association with AML1. Key residues implicated in the interaction of P60 with FOXP3 have been identified and allowed us to identify P60 derived peptides with higher Treg inhibitory capacity

**INHIBITORS OF FOXP3 TRANSCRIPTION FACTOR**

**FOR CANCER THERAPY:** Mechanism of action and sequence optimization of peptide P60

**Intellectual Property**

New Patent application to be filed.

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