cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

Inhibitors of FOXP3 Transcription Factor for cancer therapy

- Immunoregulatory function of T regulatory cells (**Treg**) 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 it is considered its "master regulator".
- Inhibition of **FOXP3-NFAT interaction** might lead to the impairment of specific functions of FOXP3 and Treg activity and thus, be beneficial in the development of vaccines and tumor therapies.
- **F39,** a peptide able to disrupt Foxp3/NFAT interaction has been found:
  - F39 interferes with the ability of FOXP3 to repress expression of IL2 and Treg immunosuppressive activity *in vitro* and *in vivo*.
  - F39 is able to improve T cell proliferation and cytokine production by effector T cells after TCR stimulation.
- A virtual screening has been conducted to select small molecules that may fit the Foxp3-NFAT hot spot and identify **new pharmacological compounds**. Experimental assay is currently *on-going*.
- **Indication:** Chronic viral infections (HBV), Cancer (prostate, colorectal, breast…).

Novel Approach

- To establish a proof of principle for a new strategy to inhibit Treg cell activity by inhibiting Foxp3/NFAT interaction.
- There are no available compounds able to inhibit Treg activity. *In vivo* inhibition of Foxp3/NFAT interaction by F39 has shown antitumor activity in different tumor cells in mice.

Target Identification

- NFAT plays a pivotal role in the T cell activation-induced transcriptional response during Th cell differentiation. Its interaction with FOXP3 has been shown to be crucial to repress expression of IL2, upregulate expression of the Treg markers CTLA4 and CD25, and confer suppressor function to T lymphocytes.
- F39 inhibits Foxp3-NFAT interaction, impairs the activity of this cooperative complex (regulation of cytokine production by effector T cells, and immunosuppressive activity of Treg cells) and enhances T cell proliferation and cytokine production upon TCR stimulation.
- F39 exibited antitumor efficacy in different mice tumor models.
- F39 has been identified as a T_{reg} function regulator and a potential agent for tumor immunotherapy.

Target Validation

- ***In vitro,*** F39 binds to NFAT and inhibits Foxp3-NFAT interaction, improves cytokine production by effector T cells upon TCR stimulation and Impairs the Suppressor Function of FOXP3-Expressing.

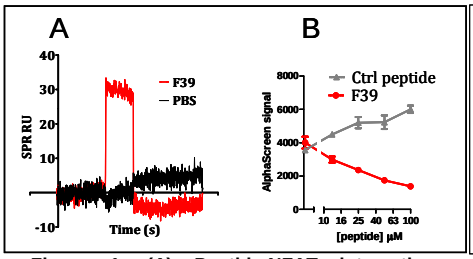

Figure 1. (A) Peptide-NFAT interaction measured by Surface Plasmon resonance. (B) Inhibition of NFAT/FOXP3 interaction measured by Alfascreen.

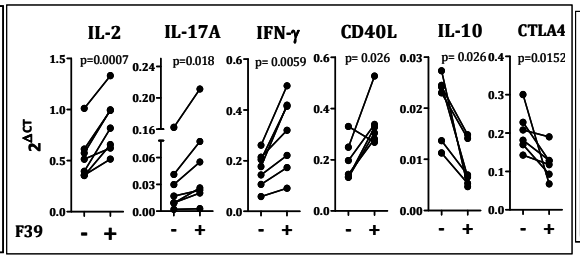

Figure 2. F39 modulate cytokine mRNA expression in human CD4 T cells (from different healthy donors) after TCR stimulation.

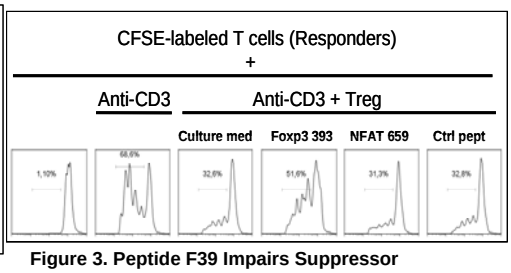

Figure 3. Peptide F39 Impairs Suppressor Function of FOP3-Expressing Cells.

- ***In vivo,*** F39 exhibited antitumor efficacy in different mice tumor models.

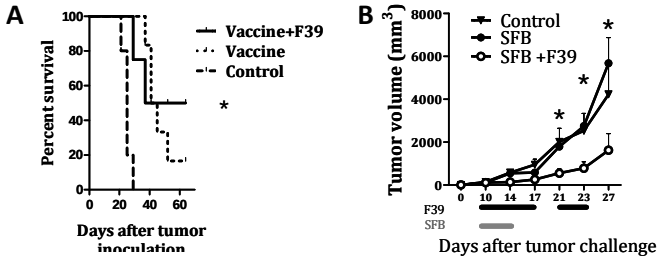

Figure 4. (A) F39 improved antitumor efficacy of a vaccine in TC-1 tumor model. (B) F39 improved antitumor efficacy of Sorafenib in Hepa129 hepatoma tumor model.

New Agents

Structure-activity relationship generated, together with structural information from plausible binding mode has been used to conduct a virtual screening. Selected small molecules, that may fit the Foxp3-NFAT hot spot, are currently being assayed.

Intell. Property

Patent application to be filled.

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