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.
- CM-1351, a peptide able to disrupt Foxp3/NFAT interaction, has been discovered as chemical probe to validate this approach:
  - CM-1351 interferes with the ability of FOXP3 to repress expression of IL2 and Treg immunosuppressive activity in vitro and in vivo.
  - CM-1351 improves T cell proliferation and cytokine production by effector T cells after TCR stimulation.
- Based on information from CM-1351, a virtual screening has been conducted to select small molecules that fit the identified Foxp3/NFAT hot-spot. Small molecules have been identified as hits fulfilling activity criteria in four different experimental in vitro assays as Treg inhibitors (e.g. CM-1129)
- **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.
- CM-1351 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.
- CM-1351 exhibited antitumor efficacy in different mice tumor models.
- CM-1351 has been identified as a Treg function regulator and a potential agent for tumor immunotherapy.

**Target Validation**
- **In vitro**, CM-1351 binds to NFAT and inhibits Foxp3-NFAT interaction, improves cytokine production by effector T cells upon TCR stimulation and Impairs theSuppressor Function of FOXP3-Expressing.
- **In vivo**, CM-1351 exhibited antitumor efficacy in different mice tumor models.

**New Agents**
Structural data from plausible binding mode together with structure-activity relationship, obtained from exploration around CM-1351, have been used to conduct a virtual screening. Small molecules have been identified as hits (e.g. CM-1129) and are currently being tested in different assays.

**Intell. Property**
Patent application to be filed.

Contact: Business development | Email: bdcima@unav.es ; Tel: +34 948 194 700