Research Project Proposal

Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 14 ASIGNADO

Title: *Mechanisms and antileukemic efficacy of combined therapies based on the functional activation of PP2A in acute myeloid leukemia. Role of PP2A regulatory subunits as specific targets.*

Department/ Laboratory: *Laboratory of Acute Leukemias (Laboratory 1.03), Hematology-oncology Program, CIMA.*

Director 1: *María Dolores Odero*

Contact: *modero@unav.es*

Codirector: *Carmen Vicente*

Contact: *cvicente@unav.es*

Summary

Acute myeloid leukemia (AML) is an aggressive form of leukemia associated with poor prognosis. Most patients are older than 60 years, and in this group only 5-15% of cases are cured; therefore, it is urgent to develop more effective therapies. In recent years, new targeting drugs such as venetoclax (an inhibitor of the BCL-2 anti-apoptotic protein) have been developed for AML treatment. However, these drugs are not effective in monotherapy due to the high clonal heterogeneity of this disease. Only when combined with other drugs, the survival and the percentage of patients who respond to treatment improve significantly. Protein phosphatase 2A (PP2A) is a tumor suppressor that controls most signaling pathways and is inactivated in ~70% of AML cases. It comprises a scaffolding subunit, a catalytic subunit, and a variable regulatory subunit, which dictates substrate specificity. Pharmacological restoration of PP2A activity has anti-leukemic effects in vitro and in vivo. Since PP2A promotes apoptosis by affecting the phosphorylation state of a variety of pro- and anti-apoptotic factors, we hypothesized that combining FTY720 (PP2A activator) with venetoclax (BCL-2 inhibitor) might induce synergistic anti-leukemic effects. In fact, our preliminary results show that the combined treatment induces a potent synergistic pro-apoptotic activity in AML. Our aims in this project are: (1) To investigate the molecular mechanisms responsible for the synergistic effects observed when BH3-mimetic drugs and PP2A activators are combined in vitro, in vivo and in primary AML cells. (2) To identify the PP2A-regulatory subunits involved in those molecular mechanisms by using the CRISPR/Cas9 editing system.

yes	**X**
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?