



Research Project Proposal
Academic year 2021-2022
MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Project Nº 24 ASIGNADO		
Title: Combinatorial Immunotherapies in sarcomas in a novel GEMM platform		
Department/ Laboratory Division of Oncology. Solid Tumors. Lab 2.01. (CIMA)		
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<p>Summary:</p> <p>Sarcomas are rare tumors that account for 20% of children neoplasms and are responsible for 13% of cancer related deaths in youngsters <19 years old. Stagnant therapeutic regimens over the past 40 years have been the result of insufficient translational research as a consequence of small clinical series and the paucity of <i>bona fide</i> preclinical models. We have recently developed a new platform of sarcoma genetically engineered mouse models (GEMM) using CRISPR/Cas9 technology and we have implemented models with concurrent mutations mimicking more closely the human mutational landscape. We hypothesize that the use of GEMM represents a unique opportunity to identify combinatorial immunotherapies which could attain unexpected therapeutic benefits superseding the current standard of care in sarcomas.</p> <p>The project is designed to reach 3 main objectives:</p> <p>In aim 1, we will specifically characterize different GEMM sarcoma models with different mutational landscape in terms of tumorigenesis and metastasis. We will perform a systematic histological analysis and we will preserve contextual autochthonous clonal evolution in immunocompetent microenvironment in mouse-derived allografts. We will also characterize the prometastatic activity in these autochthonous models.</p> <p>In aim 2, we seek to identify the molecular determinants of tumorigenesis and metastasis in these models using a double approach: 1) At the transcriptomic level, we will perform RNA-seq comparing GEMM-derived tumors and metastases from different mutants. Validation of murine signatures and human cross-comparison will be performed by GSEA in our previously studied cohort of patients and other cohorts. 2) We will dissect epigenetic mechanisms involved since some edited genes display a chromatin remodeling function.</p> <p>In aim 3, we will systematically characterize combinatorial immunotherapies. The most successful combination will be used in <i>bona fide</i> GEMMs.</p> <p>The results of this project will lay a bedrock foundation for novel treatment approaches which will be translated to the clinical setting with the goal to increase patient survival in the treatment of prototypic sarcomas. This approach will open new avenues for the treatment of other sarcomas firmly advancing towards a so cherished personalized medicine.</p>		
yes	X	Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?
no		