Research Project Proposal
Academic year 2018-2019

Project Nº 6

Title: Unraveling the pathogenesis of human multiple myeloma by integrative multi-OMICS and single-cell RNA-seq studies in transgenic mouse models

Department/ Laboratory: Laboratory of lymphoproliferative disorders. Division of Hematological Oncology. CIMA

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Summary

Multiple myeloma (MM), a neoplastic plasma-cell disorder, evolves from a pre-malignant condition termed monoclonal gammopathy of unknown significance (MGUS), defined by the progressive accumulation of clonal plasma cells in the bone marrow (BM) without organ damage. During the last decade, the approval of new classes of therapeutic agents administered in combination with conventional drugs and autologous stem cell transplant have led to deeper remissions and durable clinical responses that extended life for most MM patients. However, the disease remains incurable, and accounts for 20% of all deaths from hematological cancers. Studies to understand how pre-malignant MGUS transits into malignant MM may lead to develop early intervention approaches with curative intention. However, such studies are hampered by the lack of valid experimental models recapitulating MM development. The work of our group is based on the generation and characterization of experimental mouse models of mature B-cell malignancies (1-7). To model MM development in mice, we conducted a systematic in vivo cre-LoxP-based screen by inducing the combination of eight gene mutations common in MM patients (i.e.: NF-κB, Ras, Myc, cMaf) at two different stages of B-cell differentiation. In young mice carrying different mutant combinations, progressive BM disease classified as MGUS-like was observed, which eventually induced fatal MM at older ages (Figure 1). Therefore our models recapitulate the natural history of human disease, including the transition of MGUS into MM and the genetic heterogeneity of the patients. In this multidisciplinary project, we will use these unique immunocompetent models to define how tumor-cell intrinsic features modulate the interaction with BM immune cells to promote MGUS transition into MM. Within our Hemato-Oncology Department, high-throughput cellular and molecular analyses including single-cell RNAseq will be conducted in both mouse and patient samples. We will also evaluate in the genetically heterogeneous mice in vivo responses to targeted drugs and immunotherapeutic agents that are in parallel being tested in clinical trials in MM patients. We expect this integrative research proposal will unveil the natural history and the biology underlying plasma cell tumor development, eventually contributing to accelerate the cure of MM.

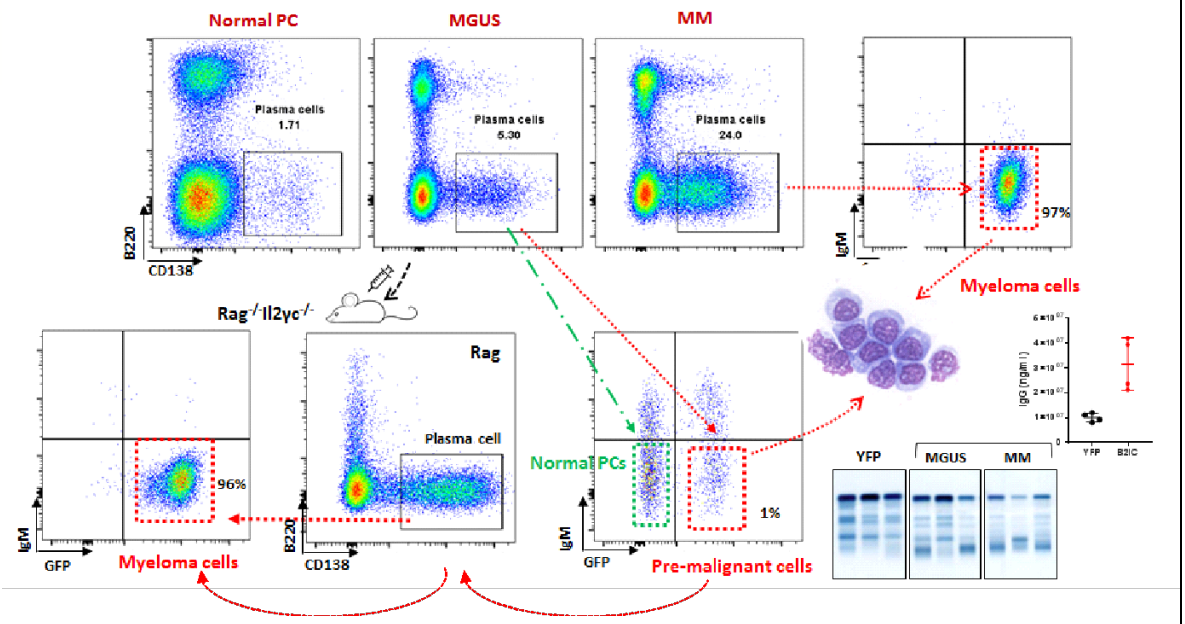

Figure 1. Generation of MGUS-to-MM models in genetically engineered mice

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yes	**x**
no	

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