Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2017-2018

Project Nº 17 ASIGNADO

Title: Exploring molecular mechanisms of germinal center-derived lymphomagenesis

Department/ Laboratory:
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Summary

BACKGROUND: Lymphomas are a heterogeneous group of cancers that arise from mature lymphocytes. Diffuse large B cell lymphoma (DLBCL) is a human mature B cell malignancy whose suspected cell of origin is a B cell transformed during its transit through the Germinal Center (GC)[1]. Considerable advancement in our understanding of the pathogenesis and progression of DLBCL has been achieved through the molecular dissection of the malignant cells, which has primarily identified recurrent genetic alterations and intracellular deregulated pathways[1,2].

GOALS: Our translational proposal aims to understand the cooperation of recurrent "driver" genetic events (p53 inactivation, addiction to NFkB and failure to terminally differentiate) with "booster" aberrant mechanisms (e.g. AID-dependent hypermutation and double-strand breaks) that make GC B cells particularly prone to genomic instability and neoplastic transformation.

METHODOLOGY: To achieve this we propose to use two novel conditionally multi-transgenic mouse models recently generated at our lab (the pBIC and the pBIC9 mice), which seem to closely resemble molecular and clinical features of human DLBCL (pBIC) and further carry constitutive expression of Cas9 (pBIC9) to facilitate in vivo genome editing applications. We will use molecular biology techniques to design and construct appropriate sgRNAs, cellular biology techniques to demonstrate in vitro the efficiency of cas9-mediated editing, and autologous HSCs transplantation techniques to explore in vivo the impact of sgRNA targeting of lymphoma B cells.

References

1- Lenz, G. & Staudt, L.M. Aggressive lymphomas. N Engl J Med 362, 1417-1429 (2010).
2- Sagardoy, A., et al. Downregulation of FOXP1 is required during germinal center B-cell function. Blood 121, 4311-4320 (2013).