Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 27

Title: Characterization of Key Epigenetic Targets in Hepatic Fibrosis and Hepatocellular Carcinoma Development. Generation of New Antifibrotic and Antitumoral Drugs

Department/ Laboratory Departamento de Bioquímica y Genética y Programa de Hepatología CIMA.

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Summary

Liver fibrosis represents a common pathogenic condition in most chronic liver diseases (CLDs) and cirrhosis, its end stage, is a huge healthcare burden. Hepatocellular carcinoma (HCC) develops on this background of CLD as a multistep process in the context of chronic inflammation and cirrhosis. Despite all the progress in understanding the molecular mechanism of liver fibrosis and hepatocarcinogenesis, there are no effective therapies to halt fibrosis or quell liver cancer. Exposure to environmental factors and the disease progress itself trigger adaptative epigenetic mechanisms, including alterations in DNA methylation or post-translational modification of histones, which control gene expression and ultimately cellular behaviour in ways critical for the development of CLD and HCC.

Enzymes carrying out these epigenetic events, such as DNA and histone methyltransferases, present altered expression and activity in CLD and HCC. The deposition of methyl marks on histones and DNA are very dynamic enzymatic processes amenable to pharmacological intervention and therefore constitute attractive therapeutic targets.

The project would address two main objectives:
1. Comprehensive analysis of the expression, activity and pathological significance of DNA and histone methyltransferases: DNMT1 and G9a, in situations of Hepatic Stellate Cell (HSC) activation or HCC cell lines in vitro and in CLD and HCC animal models.
2. Evaluation of the antifibrotic and antitumoral properties of new DNA and histone methyltransferase specific inhibitors developed in our Institution with a good safety profile. These new epigenetic therapies could be used to prevent CLD progression, and to treat HCC alone or in combination with existing drugs.

References

1. **Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design.** Llovet JM, Hernandez-Gea V. Clin Cancer Res. 2014 Apr 15; 20(8):2072-9.
2. **Epigenetics in Liver Disease.** Mann DA. Hepatology. 2014 Oct; 60(4):1418-25.
3. **G9a, a multipotent regulator of gene expression.** Shankar SR, Bahirvani AG, Rao VK, Bharathy N, Ow JR, Taneja R. Epigenetics. 2013 Jan; 8(1):16-22.

POSSIBILITY OF PhD

YES*
* (PhD grant required)