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Title of the project: *Oncostatin M, tumor associated macrophages and acquired immunity in NAFLD/NASH - related hepatocellular carcinoma*.

Background
Non-alcoholic steatohepatitis (NASH), the progressive form of non-alcoholic fatty liver disease (NAFLD), is the most rapidly rising cause of hepatocellular carcinoma (HCC) worldwide. The mechanisms responsible for NASH-related HCC development are largely unknown and biomarkers to predict the individual risk of HCC are lacking. NASH-related HCC development is multifactorial and very complex, with peculiar innate and acquired immunity changes making this tumor different from HCC with other etiologies and having lower responses to current therapies.

Hypothesis
On the basis of preliminary data we propose that oncostatin M (OSM), a procarcinogenic cytokine selectively overexpressed in human and murine NASH-related HCC, can modulate the behavior of innate and adaptive immunity, possibly contributing to the emerging peculiarity of NASH-related HCC.

Aims
By integrating competences of basic and clinical scientists, we will investigate how OSM can affect innate and adaptive immune cell behavior during the development of NASH-related HCC and define OSM prognostic significance in relation to HCC risk in NASH patients.

Experimental Design
The project is structured on three integrated tasks. Task 1 will mechanistically investigate OSM procarcinogenic role in relation to innate and acquired immunity in murine NASH-related HCC (DEN/CDAA protocol) by employing mice carrying OSMRβ conditional deletion in hepatocyte or myeloid cells. Interventional studies will administer anti-PD1 antibodies to investigate OSM interactions with the PD1/PDL1 pathway. Murine serum/plasma samples and liver specimens will be used for biochemical and molecular biology and morphological analyses. The Hyperion imaging system will allow identification/characterization of hepatic cell subpopulations and their interrelationships in the spatial context, to uncover new biomarker correlations. Task2 will investigate in vitro, ex vivo and in vivo experiments, the biological role of OSM in modulating macrophage phenotype along with the response of acquired immune cells (Aim 2.1) and in promoting interactions between different hepatic cell populations (Aim 2.2). Aim 2.3 will test in vivo the possibility to interfere with OSM for affecting the TAMs and lymphocytes behaviours in xenograft experiments. Task 3 will investigate levels of OSM and other mediators identified in Task 1 and Task 2 in serum/plasma and liver specimens from NASH patients with advanced fibrosis/cirrhosis, carrying or not HCC and evaluate their significance in relation to prognosis, recurrence, outcome and survival in order to define their prognostic relevance for NASH progression to HCC.

Expected Results
We expect to disclose: a) the role of OSM in modulating innate and adaptive immune responses in NASHrelated HCC as well as to define the prognostic significance of circulating OSM as markers for HCC risk in NASH patients; b) the impact of targeting OSM in improving current therapeutic strategies for NASH-related HCC.

Impact On Cancer
Due to the high prevalence of NAFLD/NASH in the general population, the data generated by this project will respond to the urgent need for reliable biomarkers to predict the individual risk of HCC development in NASH patients as well as to develop more effective treatments for this HCC form that is often diagnosed in an advanced stage and has a poor response to current therapies.