UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title **Next-generation NSAIDs for aging-related non communicable inflammatory diseases**

2) Abstract (max 500 words)

Inflammation and immune response are hallmarks of cancer development, progression and recurrence, and increased COX-2 expression is thought to play a role in the pathogenesis of many age-related diseases including cancer. Several studies support a role for COX-2-derived PGE2 and the TXA2/TP receptor system in critical steps of malignant tumorigenesis such as angiogenesis, cell invasiveness and immune suppression. Remarkably, there is evidence that traditional non-steroidal anti-inflammatory agents (NSAIDs) contribute to regulate tumor evasion of immunity also by decreasing the expression of Programmed cell Death 1 Ligand 1 (PD-L1) in cancer cells. However, the role of PD-L1 expressed in tumor microenvironment cells including endothelial cells in the regulation of immune responses has been poorly explored.

In the setting of a multidisciplinary project involving pharmacologists and medicinal chemists, we recently developed novel bifunctional compounds that selectively inhibit COX-2-derived PGE2 while showing platelet TP receptor antagonism in the high nanomolar range. This novel class of anti-inflammatory compounds could mitigate the side-effects of NSAIDs and coxibs on the gastrointestinal and cardiovascular system.

Based on this background and on recent data from our laboratory showing that PD-L1 is expressed and released by endothelial cells (EC) in a soluble form (sPD-L1) in response to inflammatory cytokines and VEGF, this project is aimed to profile the antitumor potential of selected COX-2 inhibitor/TP antagonist alone or in combination with anti-VEGF/anti IL-1β agents. Specific endpoints include:

1) to assess PD-L1 functional regulation in cancer cells and ECs (e.g. HUVECs and microvascular endothelial cells) exposed to exogenous IL-1β or VEGF. The expression and trafficking of PD-L1 will be measured by western blot, flow cytometry and ELISA. Functional assays will include endothelial-leukocyte co-culture experiments and cytokine release.

2) to evaluate trans-endothelial migration of cancer cells overexpressing COX-2 and/or TP receptor (e.g. MDA-MB231, HT29, HCT116) as a model of cancer cell invasiveness.

Since activated platelets can trigger chronic inflammation and support tumorigenesis via the release of soluble mediators, such as TXA_2 and VEGF, selected co-culture experiments will be performed.

In vivo studies in mouse models of cancer will be carried out in collaboration with Prof. Patrignani's laboratory (University of Chieti). The expression of COX-2 and PD-L1 will be measured in tumor biopsies from breast and colorectal patients.

This project will contribute to better profile the anti-inflammatory and immune-modulating properties of novel agents with potential applications in combined anti-cancer therapies. An additional goal of the project is to characterize the endothelium, namely mature endothelial cells, as a source of PD-L1/sPD-L1 and more generally as an immunological barrier.