Title: FIBROmeltIN: TARGETING FIBRONECTIN IN MYELOFIBROSIS

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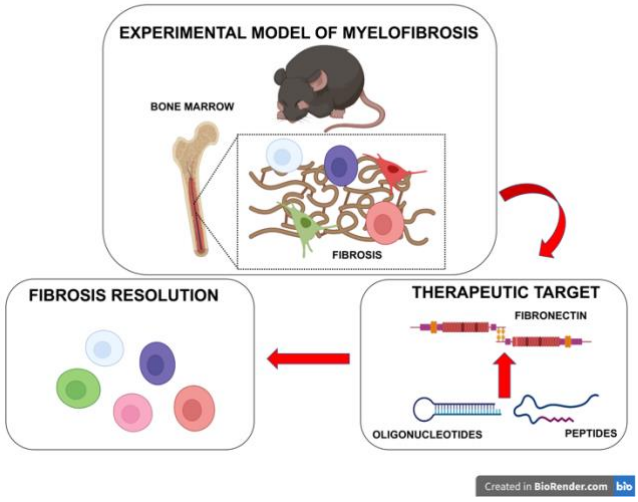
Research Theme/Topic: HEMATOLOGY/ONCOLOGY

Background: Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by an increased number of atypical megakaryocytes, progressive fibrosis in bone marrow and splenomegaly. Bone marrow fibrosis is the consequence of excessive deposition of extracellular matrix by stromal cells in response to secreted pro-inflammatory and pro-fibrotic cytokines from proliferating megakaryocytes. In patients with PMF, high fibrosis grade is associated with worse prognosis. To date, therapeutic attempts of bone marrow fibrosis reversal have demonstrated only limited success. Fibronectin (FN) is a glycoprotein that mediates the assembly of other extracellular matrix proteins and regulation of growth factor activity to direct myofibroblast differentiation and neo-angiogenesis. FN homeostasis is significantly dysregulated in myelofibrosis and FN fibres represent a major component of the fibrotic scar. Thus, in this project we propose an integrated targeting strategy to reduce FN deposition and polymerization *in vivo* in mouse models of myelofibrosis. The primary outcomes of this project will be to assess whether preventing FN fibril assembly, ablation of its expression, and combination thereof will result in the reversal of the altered bone marrow microenvironment and fibrosis in mouse models of myelofibrosis. Successful completion of the proposed translational study will provide new targeting strategies to treat and/or manage myelofibrosis effectively.



Techniques: Bone Marrow isolation, Cell cultures, Immunofluorescence, Western blot, Flow Cytometry, Cell Sorting, ELISA, Immunohistochemistry, Animal Models, qPCR, Gene Silencing.