**PROJECT**

**Supervisor:** __Giovanna Musco_____

Title: *Pharmacological targeting of HMGB1-CXCL12-CXCR4 axis*_____

*Curriculum*: _____ Biologia Cellulare e Molecolare

_____

| | |
|---|---|
| Link to the personal page of the University or relevant hospital site website: | https://research.hsr.it/en/divisions/genetics-and-cell-biology/biomolecular-nuclear-magnetic-resonance/giovanna-musco.htm |

**Description of the Project (max 3,000 characters including spaces)**

**Background/gap of knowledge**

HMGB1 is a key molecule that both triggers and sustains inflammation following infection or injury, and is involved in a large number of pathologies, including cancer. HMGB1 participates in the recruitment of inflammatory cells, forming a heterocomplex with the chemokine CXCL12 (HMGB1·CXCL12) (1), thereby activating the G-protein coupled receptor CXCR4. Identification of molecules that disrupt this heterocomplex and/or can interfere with the HMGB1/CXCL12/CXCR4 offer novel pharmacological opportunities to treat inflammation-related diseases.

Work performed in our lab has shown that indeed the HMGB1●CXCL12 heterocomplex is druggable and that the salicylate derivative diflunisal (DFL) is able to target and disassemble the HMGB1●CXCL12 hetero-complex and to block immune cell recruitment (2).

**Rationale and hypothesis**

The targeting of chemokine-based heterodimers and of their interaction with their cognate receptor is emerging as a novel approach to specifically modulate inflammatory responses. This strategy might represent a more selective alternative to CXCR4 direct blockade, which often leads to chemoresistance . We thus hypothesize that the targeting of HMGB1•CXCL12•CXCR4 might be profitably used in inflammation related cancers such as malignant mesothelioma (MM). However, the downstream effects underlying the HMGB1•CXCL12 interaction with CXCR4 and of its pharmacological inhibition are still elusive.

**Objectives and specific aims**

In this project the candidate will study

1. the effects of DFL vicinal pathways elicited by the interaction of HMGB1●CXCL12 with CXCR4
2. the effects of DFL on endpoint of HMGB1●CXCL12●CXCR4 related pathways
3. investigate the effect of DFL in combination with existing therapies against a preclinical malignant mesothelioma mouse model.

**Expected outcomes**

Define the signalling mechanisms governed by the HMGB1•CXCL12•CXCR4 complex and clarify how its pharmacological inhibition modulates this axis.

Generate new therapeutic insights for inflammation-related cancers, using multiple myeloma (MM) as the primary model.

Provide pre-clinical evidence that the inexpensive drug DFL can delay MM progression and improve survival.

**Skills that the student should acquire** (max. 600 characters including spaces):

The PhD student will develop expertise in preclinical cancer models, GPCR signaling biology, advanced cell signaling assays, and transcriptomics/bioinformatics, making them well trained for careers in cancer biology, drug discovery, or translational biomedical research.

**References** (max. 15)

(1) Mantonico et al. The acidic intrinsically disordered region of the inflammatory mediator HMGB1 mediates fuzzy interactions with CXCL12 Nat. Comm. https://doi.org/10.1038/s41467-024-45505-7

(2) De Leo et al. Diflunisal targets the HMGB1/CXCL12 heterocomplex and blocks immune cell recruitment EMBO Reports (2019)20:e47788