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PhD student position

Design and synthesis of multifunctional agents targeting the hematopoietic niche in chemoresistant myeloid leukemia.

Position to be filled in October 2021

Context and objectives of the thesis:

Today, the predominant role of STAT5 proteins is established not only in the genesis of leukemia, but also in self-renewal and quiescence of normal and leukemic hematopoietic stem cells. Targeting leukemic stem cells (LSC) and eliminating their resistance to anticancer agents is a major challenge in the treatment and eradication of myeloid leukemia. Since 2013, our research has enabled us to identify lead compounds exhibiting strong antiproliferative activities on myeloid leukemia cell lines but also increasing their sensitivity to conventional chemotherapy agents.[1-4]

Leukemia, myeloproliferative and myelodysplastic syndromes are the leading cause of cancer in children under 15. Among these diseases, acute myeloid leukemia (AML) remains difficult to cure because relapse occurs often after conventional treatment.[5] Indeed, within the hematopoietic niche, some cells have acquired the properties of stem cells (LSC, leukemic stem cells) .[6] The development of innovative targeting therapeutic strategies to eradicate, within the hematopoietic niche, leukemic stem cells (LSCs), which play a major role in drug resistance and the recurrence of leukemia, is essential to improve the outcome of treatments. Numerous proteases, such as cathepsin B, are present in the hematopoietic niche, in which LSCs play a major role in drug resistance and recurrence of myeloid leukemias.[7] The multifunctional agents considered should enable by enzymatic cleavage. the precise delivery into the haematopoietic niche of inhibitors acting in synergy, specific for proteins such as DYRK1A/B kinases and the transcription factor STAT5.[8,9] These proteins are involved in cell control and are identified as relevant targets for the treatment of cancer, in particular leukemia.

During this thesis project, associating IMT and SOL teams of EA7501 GICC, two inter-complementary work axes are envisioned: i) design and synthesis of original chemical links (enzymatic release systems) selectively cleavable by proteases present in the hematopoietic niche (e.g. cathepsin B), ii) development of multifunctional agents containing two types of inhibitors, connected by a protease cleavable linker, which will act in synergy by targeting for instance DYRK1A/B kinases (loss of the quiescence of LSCs) and STAT5 transcription factor (eradication of re-sensitized LSCs).

These structures are willing to engender a synergistic effect on leukemia cells, in particular LSCs, partly responsible for the resistance of the disease and the relapse.

Environment:
The IMT (Molecular and Therapeutic Innovation) team of the GICC has already demonstrated its know-how to develop, in collaboration with Dr Gouilleux of the SOL team (Oncogenic Signaling and Leukemogenesis), inhibitors of the STAT5 transcription factor with sub-micromolar anti-leukemia (thesis L. Juen, M. Polomski). Currently, an FRM project allows us to study a co-culture model of hematopoietic niche. The IMT team also has strong expertise in the development of chemical linkers cleavable by protease in various projects (coll. Dr Joubert, member of Labex MabImprove) .[10] Finally, preliminary work carried out (LabEx SynOrg project) in partnership with Dr Gouilleux and Pr Besson, specialist in DYRK kinases in Rouen,[11] have already enabled us to identify two main strategies in the design of multifunctional agents targeting DYRK1A/B and STAT5.

Required profile:
The applicant, from university or engineer school, possesses solid knowledges in organic and medicinal chemistry. He is motivated to work closely with biological partners.

Application:
CV, cover letter, grades and ranking in M2.
Two recommendation letters (or contact information of at least 2 references).
NB : It is compulsory to apply on ADUM.

Application deadline: june 1, 2021.

References:
(1) Juen L. *et al. J. Med. Chem.* **2017**, 60, 6119. (2) Polomski M. *et al. ChemMedChem* 2021, 16, 1034. (3) Brachet-Botineau, M. *et al. Cancers* **2019**, *11*, 2043. (4) Brachet-Botineau, M. *et al. Cancers* **2020**, *12*, 240. (5) Tallman, M. S. *et al. Blood* **2005**, *106*, 57. (6) Mikkola, H. K. A. *et al. Nat. Biotechnol.* **2010**, *28*, 237. (7) Staudt, N. D. *et al. Stem Cells and Dev.* **2012**, *21*, 1924. (8) Friedman, E. *J. Cell. Biochem.* **2007**, *102*, 274. (9) Bunting, K. D. *et al*. *Blood* **2002**, *99*, 479. (10) Bryden, F. *et al. Org. Biomol. Chem.* **2018**, *16*, 1882. (11)Fruit, C. *et al. Pharmaceuticals* **2019**, *12*, 185.