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PhD student position

Synthesis of inhibitors targeting STAT5 proteins in the treatment of myeloid leukemia: effects on chemo-resistance

Position to be filled in September 2017

Context:

For 15 years, many experimental facts have stressed out the essential role of STAT5 protein (Signal Transducer and Activator of Transcription 5) in the genesis and maintenance of chronic myeloid leukemia (CML).[1] Inhibition of STAT5 would contribute to eliminate CML cells resistant to tyrosine kinase inhibitors such as imatinib mesylate (IM), inhibitor of the Bcr-Abl oncogene, which is primarily responsible in the origin of CML.[2] It is therefore manifest that STAT5 represents a evident therapeutic target in the treatment and eradication of this pathology.

The proposed thesis position is based on the synthesis of heterocyclic compounds inhibiting STAT5 protein, in the aim of anti-leukemic therapy.

This transversal research program, involving the UMR 7292 GICC's IMT and LNOx teams, was the subject of preliminary work which led to the lead compound **LJ274**.[3] The latter, formed by an indole moiety linked to a substituted tetrahydroquinoline ring, shows strong antiproliferative activities on CML and acute myeloid leukemia (LAM) cell lines. **LJ274** targets STAT5 phosphorylation, in leukemic cells but also increases their sensitivity to agents used in conventional chemotherapy such as IM or Ara-C.

These data show the interest in pursuing pharmacomodulations on **LJ274** in order to obtain a more stable, effective and specific inhibitor.

Objectives of the thesis:

Objective 1: Improve the anti-leukemic activity of LJ274 from µM to nM. For this purpose, and in agreement with the successive biological evaluations (cell viability, STAT5 phosphorylation), the PhD student will perform various pharmacomodulations of the new pharmacophore **LJ274**.

Objective 2: Study and improve the chemo-sensitizing effect. Some analogs having shown an action on STAT5 expression, the student will conceive by organometallic coupling new compounds bearing an alkyl-, aryl- or heteroaryl-carbonyl substituent on the tetrahydroquinoline ring. Their effects on the sensitization to chemotherapeutic agents along with the leukemic cells resistance to these agents will be analyzed.

Objective 3: Identify the inhibitors molecular target(s). The wide diversity of synthesized analogs will allow us to analyze in detail the different molecular mechanisms and to identify the effectors targeted upstream by our molecules on STAT5 activation and/or expression.

Environment:
The IMT team (Molecular Innovation and Therapeutics) is specialized in heterocyclic synthesis of compounds with anti-cancer activity. Our partner, Dr. Fabrice Gouilleux of the LNOx team (Leukemic Niche & redOx Metabolism), is expert in STAT5 signaling in hematopoiesis and leukemogenesis. This medicinal chemistry work carried out within the IMT team will contribute to the joint project of the IMT and LNOx teams: i) to improve the understanding of STAT5 signaling in leukemias, ii) to identify a drug candidate.

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).

Application deadline: April 10, 2017.

References:
(1) Bunting, K.D. *Front. Biosci.* **2007**, *12*, 2807. (2) Warsch, W. *et al*. *Blood* **2011**, *117*, 3409. (3) **Juen, L**. PhD Thesis, Tours University, 2016.