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Post-doctoral position in medicinal chemistry 24 months

Synthesis and biological evaluation of inhibitors targeting STAT5 signaling in chemoresistant myeloid leukemias

Funded by the FRM (Fédération pour la Recherche Médicale)

Position to be filled in January 2019

Context:

For fifteen years, numerous experimental facts have underlined the important role of the STAT5 proteins (Signal Transducer and Activator of Transcription 5) in the genesis of leukemias. STAT5 is involved in the self-renewal and quiescence of normal hematopoietic (HSC) and leukemic (LSC) stem cells. Targeting LSC is a major issue in the treatment and eradication of some hematological malignancies. In this context STAT5 represents a therapeutic target of choice. Inhibition of its activity would help to eliminate the impact of its factors on the survival, self-renewal and quiescence of LSC along with their resistance to anti-cancer agents.

In this aim, the proposed position is based on the synthesis of molecular structures directed towards STAT5 proteins, willing to engender effects on leukemic cells, in particular resistant LSCs, partly responsible of the disease resistance and relapse.

This transversal research program involves two partners belonging to GICC group in Tours: the medicinal chemistry IMT team where this position is offered and cellular/molecular biology LNOx team (Dr. Fabrice Gouilleux), where a biology 2 years position is proposed.

Project:

In 2012, it was demonstrated that the inhibition of STAT5 expression by a PPARγ receptor agonist originally used as an antidiabetic molecule tends to decrease the LSC pool in patients with chronic myeloid leukemia (CML). In a screening of a series of compounds from a diabetes and PPAR project, we identified a hit molecule inhibiting phosphorylation of STAT5 and proliferation of CML cells and acute myeloid leukemia (AML). This increases the effect of Imatinib (IM) in CML cells, but its antiproliferative effect is independent of PPAR and much more effective than true PPAR receptor agonists. These results, in agreement with the literature, suggest that the anti-leukemic effect of PPARγ agonists is linked to an "off-target" effect.

Given the significant side effects of drugs used in the treatment of diabetes, since removed from the market, we exploited this effect "off-target" and synthesized analogues of the hit to improve its anti-leukemic activity. We were able to identify the lead **LJ274** (Juen, L. *et al.*, *J. Med. Chem.* **2017**). The latter shows antiproliferative activities on CML and AML lines of 3 to 9 µM. It preferentially targets the phosphorylation and the activity of STAT5 but also, by its action on the

expression of STAT5, increases their sensitivity to agents used in conventional chemotherapy such as IM or Ara-C.

In this project, we are considering the synthesis of novel inhibitors of STAT5 expression and/or activation in order to re-sensitize these cells to conventional therapies. We propose to validate the STAT5 target using a leukemic cell microenvironment model based on co-cultures of leukemic cells with stromal cells, knowing that LJ274 has no effect on them. The design of analogs of LJ274 lead will mainly follow three axes: i) the bioisosteric replacement of the indole, ii) the modification of the linker, iii) various substitutions at different positions of the tetrahydroquinoline skeleton.

Biological part of the project will be performed by a second post-doctoral fellow, expert in cellular and molecular biology, recruited for two years.

Environment:

The IMT team (Molecular Innovation and Therapeutics) is specialized in heterocyclic synthesis of compounds with anti-cancer activity, along with bioconjugation technology. Our biological partners is Dr. Fabrice Gouilleux of LNOx team (Leukemic Niche & redOx Metabolism), expert in STAT5 signaling in hematopoiesis and leukemogenesis.

This medicinal chemistry work will be carried out within IMT team (24 months) in Tours and will contribute in particular to the joint project of the IMT and LNOx teams: i) to identify a drug candidate in leukemic diseases, ii) to improve the understanding of STAT5 signaling in leukemias.

Required profile:

The applicant, graduated from university or engineer school, has a PhD in organic or medicinal chemistry. He possesses solid knowledges in organic and medicinal chemistry. He is motivated to work closely with biological partners.

Salary:

2000-2100 € net/month.

Application:

CV, cover letter.
Two recommendation letters (or contact information of at least 2 references).

Application deadline: 10/12/2018

References:

LSCs: (1) Tallman, M. S. et al *Blood* **2005**, *106*, 57-69. (2) Mikkola, H. K. A. et al *Nat. Biotechnol.* **2010**, *28*, 237–238.

STAT5: (1) Cholez, E. et al *Leukemia* **2012**, *26*, 2390-2397. (2) Bourgeais, J. et al *Oncotarget* **2016**. doi: 10.18632/oncotarget.11480. (3) Bunting, K. D. et al *Blood* **2002**, *99*, 479–487. (4) Juen, L. et al *J. Med. Chem.* **2017**, *60*, 6119-6136.