**EA7501 GICC - Université de Tours**
**Equipe IMT : Innovation Moléculaire et Thérapeutique**
*Laboratoire d'excellence SynOrg*
*«Des molécules pour le vivant»*

***Research Master Degree***
*Research program proposed for 2018-2019*

# Title: Targeting acute myeloid leukemia stem-like cells.

**Supervisor:** Gildas PRIÉ, Associate Professor, **EA 7501 GICC - Eq. IMT**, University of Tours, FR.
**Collaborators:** Fabrice Gouilleux (Tours), Thierry Besson (Rouen), Laurent Meijer (Roscoff)

**Context:**

Development of innovative therapeutic strategies to eradicate cancer stem-like cells (CSCs), which play a major role in drug resistance and disease recurrence, is critical to improve cancer treatment outcomes. Acute myeloid leukemia (AML) is a typical example of this statement since it remains difficult to cure as relapse often occurs after conventional treatment. In this project, we are willing to develop multi-functional agents, which will act in synergy: (i) **targeting DYRK1A/B will promote loss of leukemia stem cells (LSCs) quiescence and enhancement of their sensitivity**, (ii) **inhibiting STAT5 will then target these re-sensitized cells**.

These so-called multi-functional agents are willing to engender a synergistic effect on AML cells, in particular resistant LSCs, partly responsible of the disease resistance and relapse.

**Project:**

We intend at developing new multi-functional agents against AML disease, which will act in synergy, by targeting DYRK1A/B to eliminate resistant LSCs quiescence therefore enhancing their sensitivity, along with inhibiting growth of these re-sensitized cells by inhibiting STAT5 protein. In this aim, we propose to use the concept of multi target ligand, promising method in therapeutics. Indeed, the project is based on the development of molecular structures containing two types of drugs, connected by a non-cleavable or a cleavable linker.


The localization of introduction of the different linkage functions on both inhibitors has already been determined in order to keep the highest biological property. The final structures will be tested by our biological partners in term of DYRK and STAT5 inhibition, along with AML cell lines growth inhibition. In the case of cleavable linkers, protease cleavage assays will be performed. First results with the two proposed types of linkage will permit us to validate the proof of concept (synergistic effect) and should help us to refine conjugation mode.

**Originality of the project:**

This project involves molecular and therapeutic innovation in the fields of heterocyclic and medicinal chemistry, *i.e.* multi-functional agents, by combining training expertise in organic synthesis, protease cleavage assays along with compounds complex analysis.

**Key topics and technologies:**

*Synthesis*: heterocyclic chemistry, multi-step synthesis, metal-catalyzed reactions, medicinal chemistry.
*Purification*: flash silica gel chromatography, automatized chromatography, semi-prep HPLC.
*Analyses*: NMR ($^{1}H$, $^{13}C$, COSY, HSQC, HMBC), GC-MS, HPLC, HRMS.

**Contact:**
Gildas Prié ☎ +33 2 47 36 72 28 💻 gildas.prie@univ-tours.fr

EA 7501 GICC - Eq. IMT Innovation Moléculaire et Thérapeutique - UFR des Sciences Pharmaceutiques
Université de Tours, 31 Avenue Monge, 37200 TOURS.