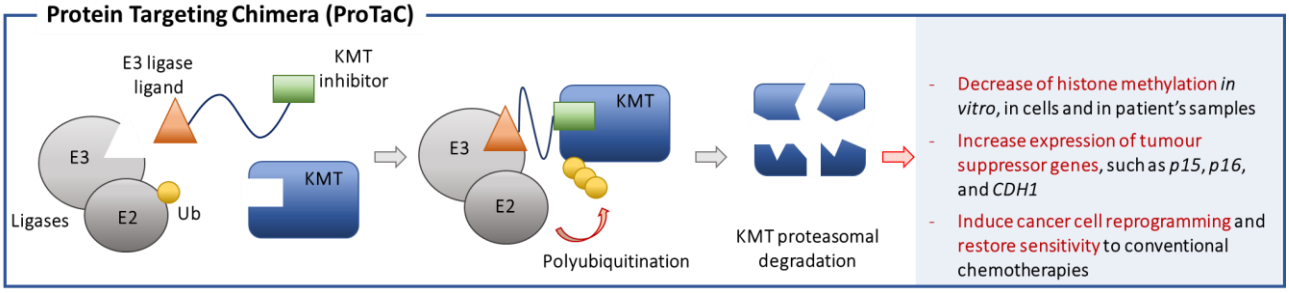
Master 2 internship Offer

PROTAC STRATEGY APPLIED TO EPIGENETIC MECHANISMS IN CANCERS

Institut des Biomolécules Max Mousseron (IBMM), CNRS-UM-ENSCM, UMR524, Montpellier
Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Montpellier

Context - Aim

Epigenetic modifications, including histone methylation, catalysed by lysine methyltransferases (KMTs), are involved in tumour formation and progression. However, despite the unquestionable role of KMT in cancers, only one KMT inhibitor (KMTi), targeting EZH2 (Tazemetostat), has to date been approved for anticancer treatments in 2020. This shows the urgent need to identify new strategies to target this epigenetic mechanism in cancer. The aim of this Master internship project is to apply the protein targeting chimers (PROTAC) strategy to target KMTs. This strategy consists in connecting a E3



ligase ligand and a KMTi to induce selective proteasomal degradation of KMT. We expect to restore a non-pathological histone methylation profile, rescue tumour suppressor gene expression in cancer cells and ultimately restore sensitivity of resistant cancer cell lines to conventional chemotherapies. This multi-disciplinary project involves organic synthesis as well as biochemical evaluation of the $PROTAC_{KMT}$.

Project

Firstly, based on reported KMTi synthesis functionalised derivatives will be synthesised, in parallel E3 ligands, carrying various linker, will be prepared applying well-described synthesis pathways. Secondly, with both functionalised moieties in hands, $PROTAC_{KMT}$ will be synthesised by amide coupling reaction and fully characterised. Finally, the evaluation of the compounds will be performed *in vitro* on purified enzymes and in cell lines. Evaluation of the lead compounds in patient samples will be carried out in collaboration. Overall, we expect to restore a non-pathological histone methylation profile, rescue tumour suppressor gene expression in cancer cells and ultimately restore sensitivity of resistant cancer cell lines to conventional chemotherapies. This multi-disciplinary project involves organic synthesis as well as biochemical evaluation of the $PROTAC_{KMT}$.

Candidate profile

The candidates must have completed their master's degree in chemistry. Very good practical skills in multi-step organic synthesis and organic compound characterisation (NMR, IR, HPLC, LC-MS) are required. An experience in life biochemistry/biology would be appreciated.
The candidates should be highly motivated, inquisitive, geared towards problem solving, and capable of dealing with new concepts and challenges in order to conduct this highly inter-disciplinary work.
Fluent level in French or English is required.

This 6-month M2 fellowship is supported by the Key Initiative MUSE « Biomarkers & Therapy » and will be held in the glycochemistry and molecular recognition team at the IBMM. Short stays at the IRCM can be envisaged.
The candidates must send their application including CV with at least one reference, cover letter and their master's results as soon as possible and before **30 November 2021**.

Contact

Dr Marie Lopez (marie.lopez@cnrs.fr)