Fiche de Poste
Ingénieur d'études en chimie organique de synthèse

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Title	New protein degraders (PROTACs) for triggering ferroptosis in acute myeloid leukemia cells
Keywords	PROTAC, ferroptosis, acute myeloid leukemia (AML)
Required skills	Synthesis, purification and characterization of organic molecules ; physcochemical characterizations (solubility, logP).

Project context:

Acute myeloid leukemias (AML) are associated with a poor prognosis and their resistance to treatments necessitates new therapeutic modalities. Having identified a novel target in AML, we propose the design of original molecules acting as protein degraders (PROTACs) of this target, and capable of circumventing the resistances phenomena that are classically observed in these pathologies.

PROTACs are heterodimeric compounds displaying two ligands connected through a linker. One is a ligand for a protein of interest (POI) that is to be degraded, and the other one for an ubiquitin-E3 ligase (Ub-E3). **PROTACs enable the hijacking of the ubiquitin-proteasome system to degrade a protein involved in a pathological process**. To be fully functional, it must allow the recruitment of POIs and Ub-E3 in a finely controlled spatial arrangement. Therefore, a library of PROTAC emcompassing the use of multiple linkers of different lengths and compositions will be prepared and our biologist collaborator in the Institut de recherche St Louis (Paris) will evaluate them. In addition to the optimization of the linker, different E3 ligase ligand will be surveyed. Altogether a collection of 40-60 compounds will be synthesized and the best performing compound will be further optimized in terms of efficacy, physicochemical properties and if possible pharmacokinetic parameters.

Expected outcome:

We envision the discovery of 2-3 effective PROTACs which should exhibit stronger antileukemic effect compared with the parental inhibitor – this is foreseen as the suppression of the scaffolding function of the protein, in addition to its catalytic activity, should ensure a complete blockade of its biochemical pathway. The synthesized compounds will be protected by a patent application before seeking further valorization opportunities.

Applications:

Send application by email at anthony.martin@umontpellier.fr including a cover letter and a CV.