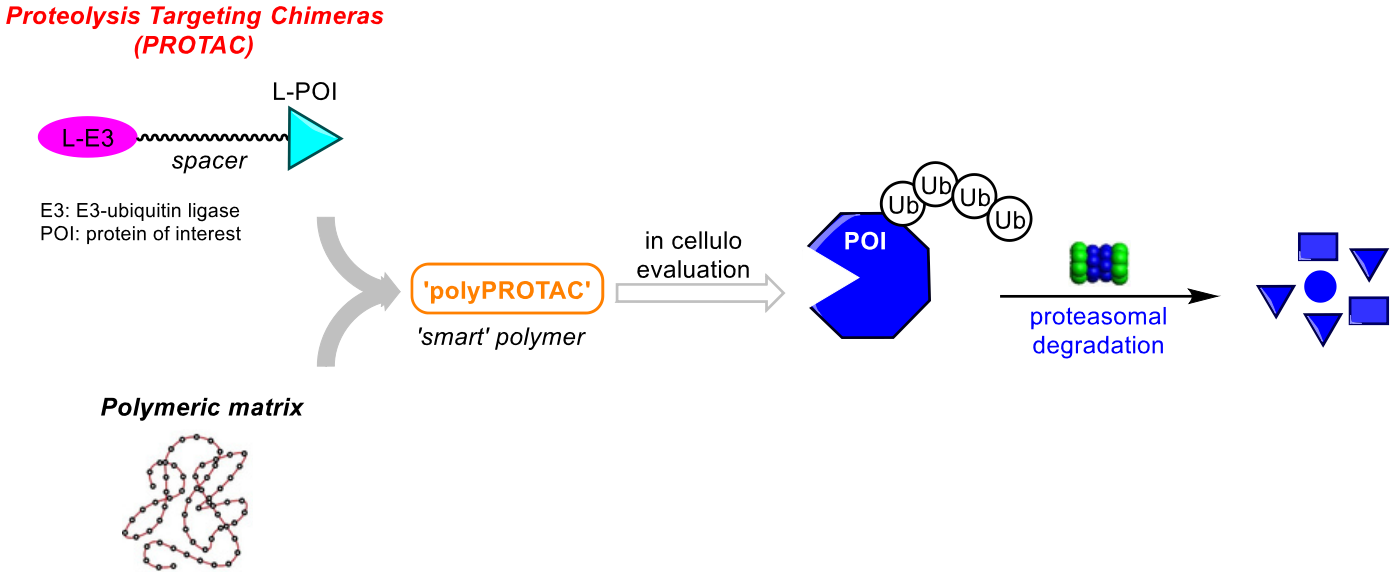
Master/3d year engineer 6 months RESEARCH INTERNSHIP
From January 2024

polyPROTAC: implementing multivalency in the design of specific proteolysis inducers.

Period: 6 months from January/February to June/July 2024
Contacts : anthony.martin@umontpellier.fr ; benjamin.nottelet@umontpellier.fr
Internship locations: IBMM, Pole Chimie Balard, Montpellier, Peptides *www.ibmmpeptide.com* & *Polymers https://ibmmpolymerbiomaterials.com*
The work will take place mainly at the IBMM in Montpellier

Summary
Recently, PROTACs emerged as a major innovation in the design of new therapeutic agents. When interfering with a protein target, conventional inhibitors resort to an occupancy-driven mechanism. In this aspect, PROTACs constitute a paradigm shift as they act through an event-driven mechanism. In fact, they allow the hijacking of the ubiquitin-proteasome system to trigger the degradation of a protein of interest (POI) by the proteasome. To enable this degradation, PROTACs are built as heterobivalent structures featuring two ligands: one for the POI and the other for an ubiquitin E3 ligase (Ub-E3). However, the design and development of PROTACs remains tedious. The molecular tether linking the two ligands plays a critical role in the efficacy of the degrader. Our project aims to solve this bottleneck by pioneering the concept of polyPROTAC. The core of the research project will be dedicated to generating bioconjugate functional polymers presenting multiple copies of PROTAC molecules. We hypothesize that allowing the multi-recruitment of proteins of interest to be degraded and of Ub-E3 ligases, should foster and efficient degradation of the former while drastically diminishing the importance of the role held by the spacer.



Student work
The master student recruited for this project will be involved in the synthesis and characterization of the ligands of both the Ub-E3 ligase and the protein of interest. He/she will also prepare the monomers bearing the PROTAC moieties, conduct their polymerisation. The molecular characterization of the ligands and of the monomers, and the physico-chemical characterization of the 'polyPROTACs' polymers will be at the centre of our investigations. Finally, the biological evaluations, and in particular the ability of polyPROTACs to degrade the protein of interest, will be performed by biologists collaborators.

Skills acquired:
1. Project management.
2. Small molecules organic synthesis and characterization (e.g. NMR, MS)
3. Polymers & biopolymer: synthesis and characterization (e.g. DLS, GPC)

Required skills and soft skills
1. Scientific English, Organic Chemistry and Analytical Chemistry Master's level.
2. Autonomy, scientific curiosity
3. Rigor, capacity for work
4. Good interpersonal skills, ability to report