Anticancer acetylenic prodrugs with selective cytotoxicity

PhD scientific context and project. The project aims at developing new molecules inspired by natural marine products acting as anticancer agents by an entirely new mechanism that we recently deciphered (unpublished data). This project will be carried out as part of a collaborative research program at the chemistry-biology-health interface involving three laboratories in Toulouse: the laboratory of Synthesis and Physico-Chemistry of Molecules of Biological Interest (SPCMIB, team of Yves Génisson - PhD co-supervisor), the Coordination Chemistry Laboratory (LCC, team of Valérie Maraval and Remi Chauvin - PhD co-supervisor), and the Institute of Pharmacology and Structural Biology (IPBS, team of Patrick Calsou and Sébastien Britton - PhD co-supervisor).

In the context of this interdisciplinary collaboration, an original series of cytotoxic chiral acetylenic lipids behaving as prodrugs in human cells was discovered. Their bioactivation into highly reactive entities is triggered by a specific enzyme, belonging to a well-identified family. The so-generated cytotoxic agents are particularly active against tumor cell lines derived from a deadly cancer resistant to conventional treatments.

Recently, we have shown that related synthetic molecules are activated by two other specific enzymes (here referred to as "actenzymes") belonging to the same family. It is now conceivable to develop new cytotoxic prodrugs selectively bioactivable by selected actenzymes with the required reaction polarity. The PhD thesis subject thus concerns the generalization of the concept of selectively bioactivable anticancer acetylenic lipids and the development of its different applications.

The realization of this project is articulated around three tasks distributed between the three laboratories. The SPCMIB and LCC teams (4 semesters) will lead the development of new chemical entities, from their design and optimization through structure-activity relationships (SAR) analysis to their synthesis using a suitable toolbox of organic reactions. The IPBS team (2 semesters) will be in charge of all biological assessments at the cellular and molecular levels.

- Task 1 / Semi-rational design and chemical synthesis of series of molecules: this phase will generate prodrug candidates designed from the structure of known natural substrates of the particular actenzymes and data from previously established structure-activity relationships (SAR). The structural prototype of the targeted molecules is formed by an alkynylcarbinol head anchored to a lipidic chain, the latter being possibly ω-functionalized in the form of a cell probe. An optimal organic synthesis approach will be developed to ensure the effective preparation of a wide range of compounds associating various lipidic skeletons with selected pharmacophores. This task is divided into four sub-tasks: development of the synthesis strategy (semester 1); design and preparation of the target prodrug candidates (semester 2); synthesis of the optimized prodrugs (semester 3); synthesis of the selected chiral prodrugs in enantiopure form along with the corresponding probes (semester 5).

- Task 2 / Cell evaluation and optimization of the activity of the molecules on a selection of cell lines: this phase will allow the correlation between the cytotoxicity of the compounds and the presence or not of the actenzyme target in order to guide the optimization of the structure of the synthesized compounds. It is divided into three sub-tasks: evaluation of prodrug candidates (semester 3); evaluation of second generation prodrugs (semester 4); implementation of the corresponding cell probes (semester 6).

- Task 3 / Validation of the therapeutic value of the molecules on tumor cell lines: in this phase, we will endeavor to demonstrate that the cell probes developed in task 2 can be used to

identify cancer cell lines on which the prodrugs show maximum selective cytotoxicity. This step will be carried out to ultimately correlate the level of bioactivation with the cytotoxic activity of the drugs. This step will also aim at translating this approach to fresh tumor samples provided by collaborators. This task will be carried out in semester 6 with the help of expert biologists.

With the possibility of adapting the planed therapeutic approach to specific cancers, i.e. to the expression of specific actenzymes, this project paves the way for personalized medicine.

Funding: this project was selected by the Federal University of Toulouse Midi-Pyrénées in response to the call for "Interdisciplinary Doctoral Allocation" to benefit from funding subjected to validation by the Occitanie Region (confirmation expected in June 2020).

Timing: starting planed October 2020, ending expected October 2023

Candidate's profile: the candidate must have a strong background in organic chemistry, with some knowledge in pharmacochemistry and therapeutic chemistry. A competence in biology will be a plus. The candidate will have to master the concepts and tools of multi-step organic synthesis with solid theoretical and practical skills in stereochemistry, reactivity, purification and structural characterization of small molecules. The candidate should be willing to spend time in a biology lab where he/she will learn tissue cell culture, cell viability assays, imaging using super-resolution microscopy that he/she will exploit to characterize the new prodrugs he/she has synthesized.

Laboratories: SPCMIB (UMR 5068 CNRS-UT3); LCC (UPR 8241 CNRS); IPBS (UMR 5089 CNRS-UT3)

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