PROJECT ATHENA: Design improvement of homogeneous Dual Antibody-Drug Conjugates to reach promising and efficient crossfire treatments of cancers

Offer type: PhD thesis
Financing: ANR / FRANCE 2030
Salary range: 1650,72 € monthly net income
Recruiting organization: UMR1100 CEPR, Team 2 “Proteolytic Mechanisms in Inflammation”, group “Immunoconjugates” (C. Denevault, N. Joubert)
Workplace: TOURS (37000) - FRANCE
Skill area: bioconjugation, therapeutic chemistry, organic chemistry, heterocyclic chemistry
The scientific activity of our “Immunoconjugates” group (ADCs: antibody-drug conjugates, etc) is based on an interdisciplinary approach ensured by chemists, pharmacists, clinicians and biologists. Our expertise in heterocyclic and medicinal chemistry ranges from the development of new organic synthetic methodologies to the bioconjugation of small cytotoxic molecules onto antibodies (mAbs) *via* a suitably constructed spacer arm (linker) to produce antibody-drug conjugates (ADCs). These skills allowed us to design and synthesize new heterobifunctional linkers, giving access to original homogeneous ADCs, from any native antibody (patented methodologies), with new mechanisms of action, new release mechanisms and/or for new applications.

PROJECT:

A grant from ANR / FRANCE 2030 (Project ATHENA) is available in our group (CEPR, Team 2), under the supervision of **Pr Caroline Denevault** and **Pr Nicolas Joubert**. This grant is dedicated to a **3-years PhD grant fellowship** (for Master 2 degree) starting ideally October 1st 2026. In our group, we design and produce homogeneous ADCs through in-house patented methodologies. We work in close collaboration with **Dr Aurélie Maisonial-Besset** (MCU-HDR), a radiochemist from Clermont-Ferrand, scientific director of the ATHENA project. Following our previous researches in oncology, we validated our best original ADC design, in comparison to the gold standard trastuzumab deruxtecan (Enhertu®) for applications in oncology against breast cancer, with an ADC as active as Enhertu® *in vivo* but more stable during plasma circulation. **The goal of this new project is to go even further by exploring the development of better bioconjugation technologies enabling to site-specifically conjugate two payloads with a single linker onto anti-HER2 trastuzumab to generate DAR 4 or DAR 8 dual ADCs.**

One of the current challenges in the field of oncology is to successfully overcome or reduce intrinsic or acquired tumor resistance to conventional stand-alone treatments (i.e. chemotherapies) that can significantly affect the therapeutic outcome for patients and promote recurrences. Thus, the development of innovative anticancer targeted therapies continues to be a challenging endeavor.
ADCs have been shown to selectively deliver highly active cytotoxic payloads to the tumor site. They are considered as game-changing drugs in the management of specific cancers, as evidenced by their remarkable anti-tumor efficacy, particularly in metastatic breast cancer (BC) for which ADCs are now approved for different subtypes of this pathology (hormone-dependent, HER2-positive or triple-negative BC). However, for such a strategy, the anti-tumoral efficacy of the cytotoxic drugs into the tumor highly depends on the plasma stability and the hydrophobicity control of the drug-linker conjugated onto the antibody used as carrier. Indeed, these two parameters play a crucial role in the preservation of the favorable pharmacokinetic and pharmacodynamic (PK-PD) properties of the ADCs. In this project, we aim at developing a chemical linker-platform allowing the efficient and simultaneous site-specific bioconjugation onto antibodies (IgG or other formats) of two complementary payloads with control of the number and of the localization of grafted linker-platforms. This strategy should allow us to create innovative and stable ADCs, with satisfactory PK-PD properties, that could carry both payloads for a targeted and synergistic action on tumors.

This project is divided in several tasks: (1) synthesis of drug-linker and bioconjugation onto mAbs to produce new immunoconjugates; (2) analysis and characterization of prepared immunoconjugates: physico-chemical properties; (3) *in vitro* evaluation of proteolytic cleavage; (4) *in vitro* characterization of antigen binding affinity and immunoconjugates internalization into antigen-positive cells; (5) *in vitro* evaluation of immunoconjugates cytotoxicity on several human cancer cell lines; (6) *in vivo* studies on different murine models. Some of these tasks will be performed in collaboration with Dr Aurélie Maisonial-Besset's team (IMOST, UMR1240 INSERM, Clermont-Ferrand) and Dr Guillaume Gabant (CBM, UPR4301 CNRS, Orléans). This project is attached to high-priority programmes dedicated to therapeutic biodrugs and antibodies (Biomédicaments Région CVL, Labex MabImprove, Cancéropôle Grand Ouest).

For this new project, the recruited PhD student will be helped and will work in synergy with a PhD student, to synthesize new linkers for their bioconjugation on different mAbs. The resulted ADCs will then be characterized and evaluated *in vitro* and *in vivo* in mouse models. **We have already all the active collaborations needed for this project**, including the biologists for the generation of antibodies and the biological evaluations of our ADCs on the particular models of interest (*in vitro* and *in vivo*), as well as chemical analysts (spectroscopy analyses of ADCs). The candidate will be in charge of the organic synthesis of the linker-payload entities. The applicant will also be responsible for the bioconjugation of the linker-payload entities onto the mAb (if needed, the know-how will be learned with a third year PhD student) and for some characterizations of ADCs (Drug-to-Antibody Ratio calculation, MS analysis). Further ADCs characterizations and biological evaluations on *in vitro* and *in vivo* models will be carried out by different partners of this international interdisciplinary scientific program.

Candidates profile:

The candidate must have a MASTER 2 degree (BAC+5) and a good knowledge of organic chemistry. Knowledge in chemical biology (bioconjugation) will be really appreciated but is not mandatory (help of an expert in our group to learn this expertise). There are great expectations for this PhD thesis and this scientific program financed by an ambitious PEPR Program (ANR/ FRANCE 2030). Therefore, we expect the candidate to be extremely motivated and able to make experiments with great care and reproducibility (needed for bioconjugation). The candidate must demonstrate a high degree of motivation for working in a stimulating interdisciplinary project, and master organic synthesis including purification techniques (flash chromatography and HPLC) and analytical techniques (especially HPLC). In the 9-10 first months of the program, the candidate will always work in synergy and in company of a third year PhD student dealing with ADC developments since September 2024.

Application procedure:

Applications should be submitted to **both** email addresses (CV + motivation letter, quotes from master and licence, possibility to write in french for French applicants):

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Keywords: bioconjugation, chemical biology, proteases, proteolytic cleavage, cancer, therapeutic chemistry, organic chemistry, heterocyclic chemistry.