DEVELOPMENT OF A NEW GENERATION OF ANTIBODY-DRUG CONJUGATES

Offer type: PhD thesis
Financing: ANR / FRANCE 2030
Salary range: 1747 € 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 is available in our group (CEPR, Team 2), under the supervision of Dr 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 2024. In our group, we design and produce homogeneous ADCs through in-house patented methodologies. Actually, using these methodologies, from trastuzumab (anti-HER2 antibody), we generated several ADCs, some of which exhibited *in vitro* a subnanomolar activity in SK-BR-3 cell line over-expressing HER2. **Following our previous researches in oncology, we want to proceed further through (1) the validation of our last original ADC designs, in comparison to the gold standard trastuzumab deruxtecan (enhertu®) for applications in oncology against breast and lung cancers, and lung metastasis, and (2) the development of better bioconjugation technologies as well.**

Pulmonary metastasis are associated with a neutrophilic and macrophagic inflammation, leading to the secretion of proteases like human neutrophile elastase (HNE) and cathepsins (B, K, L) in the tumor microenvironment. These overexpressed proteases can be used as tools to activate the release mechanism of antibody-drug conjugates (ADCs). ADCs combine a highly potent cytotoxic agent (drug or payload) conjugated onto a monoclonal antibody (mAb) directed to a tumor-selective antigen, through a suitably constructed linker, and are designed for the selective delivery of the drug to the tumor site.
The objectives of this project is to use neutrophilic inflammation (HNE, cathepsins) to release a potent cytotoxic agent into the inflammatory microenvironment of lung metastases, using a suitably designed ADC containing a protease-sensitive linker. In a previous work, we developed a neutrophile elastase-sensitive ADC targeting HER2 as a proof of concept. This know-how will be used to develop new protease-sensitive linkers in this study. Different payloads (*e.g.* auristatin or camptothecin derivatives) and bioconjugation technologies will also be tested.
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 (collaboration with NMNS EA6295, Tours); (4) *in vitro* evaluation of immunoconjugates cytotoxicity on several human cancer cell lines (collaboration with NMNS

and IRCM teams, U1194 INSERM, Montpellier); (5) *in vivo* studies on different murine models (collaboration with IMOST, UMR1240 INSERM, Clermont-Ferrand). This project is attached to high-priority programmes dedicated to therapeutic biodrugs and antibodies (ARD CVL Biomédicaments, APR IR, Labex MabImprove, Cancéropôle Grand Ouest).

For this new project, the recruited PhD student will be helped and will work in synergy with a post-doc expert in the field, 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 our post-doc) and 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 post-doc in our group to learn this expertise). The candidate must be very 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 an interdisciplinary project, and master organic synthesis including purification techniques (flash chromatography and HPLC) and analytical techniques (especially HPLC). In the first months of the program, the candidate will always work in synergy and in company of our post-doc (who defended his PhD dealing with ADC developments in December 2023).

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.