New hydrophilic polymeric structures limiting the hydrophobicity of antibody-drug conjugate (ADCs) for the optimization of therapeutic index

Offer type: PhD thesis

Financing: Loire Val Health FRANCE 2030

Salary range: 2300 € monthly gross salary

Starting date: 1st October 2026

Recruiting organizations:

1. EA 6299-PCM2E Laboratory of Physical Chemistry of Materials and Electrolytes for Energy, group of “pi-conjugated materials and polymers” (Pr B. Schmaltz)

2. UMR1100 CEPR, Team 2 “Proteolytic enzymes and their pharmacological targeting in lung diseases”, group of “Immunoconjugates” (Pr C. Denevault)

Workplace: University of Tours, TOURS (37000) - FRANCE

Skill area: organic chemistry, polymer chemistry, heterocyclic chemistry, bioconjugation, medicinal chemistry.

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

PROJECT:

Antibody-drug conjugates (ADCs) combine a very powerful cytotoxic agent with a monoclonal antibody (mAb) directed against an antigen overexpressed on the surface of cancer cells via a carefully designed chemical linker. Today, 19 ADCs (mAb-linker-cytotoxic) have been approved worldwide and successfully implemented in clinical strategies, while 200 clinical trials involving ADCs are in the recruitment phase or underway. However, despite the keen interest they have generated, most of the ADCs targeting solid tumors do not progress beyond phase 2 of clinical trials. In order to achieve greater translational success, **one of the key parameters to optimize ADCs is the control of the hydrophobicity of the linker-cytotoxic**. Indeed, hydrophobicity limits the number of cytotoxic agents that can be conjugated to an antibody without significantly degrading its pharmacokinetic and pharmacodynamic (PK-PD) properties. Furthermore, it contributes to ADC toxicity, promoting off-target uptake of the ADC within healthy cells that do not express the targeted antigen, particularly through the macropinocytosis process.
Thus, **this inter- and multidisciplinary thesis project** at the **interface of chemistry/biology/material sciences,** proposed by two complementary teams at the university of Tours (CEPR and PCM2E) aims to **design and synthesize several families of hydrophilic polymers, acting as hydrophobicity controllers, to integrate them into the linker structures used to design ADCs**. These hydrophilic polymers will then be grafted onto an original linker-cytotoxic, and these original molecular assemblies will then be conjugated to an antibody to produce different ADCs. The benefit provided by the hydrophilic polymers, in terms of apparent hydrophobicity of the ADCs, will be evaluated by HIC (hydrophobic interaction chromatography). The produced ADCs will then be tested *in vitro* and *in vivo* on non-small cell lung cancer (NSCLC) models.

For this project, the recruited PhD student will be working in **PCM2E laboratory** and will be in charge of the organic synthesis of the hydrophobicity control units for the linker-payload entities, which will then be conjugated to antibodies to produce the desired ADCs. The grafting onto the antibodies will be done in **CEPR laboratory**. Additionally to this working organization on two laboratories at Tours, the candidate will have the opportunity to participate in the in vitro tests at **the Department of Pharmacy of the University of Salerno** (Italy).

Candidates profile:

The candidate must have a MASTER 2 degree (BAC+5) and a good knowledge of organic chemistry. The candidate must be very motivated and able to make experiments with great care and reproducibility. 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) as well as good basis in polymer chemistry would be appreciated. A good command of English is also mandatory.

Host Laboratories:

The PCM2E laboratory and more particularly the group of pi-conjugated materials and polymers has a great expertise in design, synthesis and characterization of macromolecules for electronic, energy conversion and ultrasound applications. This team is developing new large molecules providing targeted properties like the control of the swelling or hydrophilicity.
Within the CEPR, the scientific activity of the “Immunoconjugates” group (ADCs: antibody-drug conjugates) 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.

Application procedure:

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

Pr Bruno Schmaltz, **PhD,**
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