DEVELOPMENT OF NEW IMMUNOCONJUGATES FOR HER2-POSITIVE BREAST CANCERS

Offer type: engineer position
Financing: Public: Centre-Val de Loire Region
Salary range: 16700-23000 € annual net income, according to the candidate experience
Recruiting organization: UMR7292 GICC CNRS - Université de Tours, Equipe « Innovation Moléculaire et Thérapeutique » (IMT)
Workplace: TOURS - FRANCE
Skill area: therapeutic chemistry, organic chemistry, heterocyclic chemistry
The scientific activity of our UMR, GICC (Genetics, Immunology, Chemistry and Cancer) is based on an interdisciplinary approach ensured by clinicians, biologists and chemists. This UMR includes 38 permanent staff. Our team « Innovation Moléculaire et Thérapeutique » (IMT, 7 permanent staff), directed by Pr. Marie-Claude Viaud-Massuard, is made up of therapeutic and organic chemists, and is part of two Labex (MAbImprove, and SYNORG). The IMT team is specialized in the design and synthesis of small heterocyclic antitumor regulators (*e.g.* kinases or STAT5 inhibitors). Our expertise in heterocyclic and medicinal chemistry ranges from the development of new organic synthetic methodologies to *in silico*-assisted lead discovery and optimization. Our team has also an expertise in bioconjugation of small cytotoxic molecules to therapeutic antibodies (mAbs) *via* a suitably constructed spacer arm (linker) to form antibody-drug conjugates (ADCs). These skills allowed us to design and synthesize new site-specific heterobifunctional linkers permitting access to homogeneous ADCs, from any native antibody (patented methodology). We also developed an analytical physico-chemical platform dedicated to ADC analysis.

Subject of the project:

A grant from the Centre-Val de Loire Region is available in our team (IMT). A part of this grant is dedicated to the recruitment of a PhD or an engineer for a 3-year project starting as soon as possible, under the supervision of Dr. Caroline Denevault. This work will focus on the development of original antibody-drug conjugates (ADCs) for the treatment of epidermal growth factor receptor 2 (HER2)-positive breast cancers.
Breast cancer is the most common cancer in European women. Among the different types of tumors, HER2-positive breast cancers are associated with an aggressive clinical phenotype and an unfavorable outcome. In recent years, the introduction of new anti-HER2 antibody-based treatments such as trastuzumab (Herceptin®) and the ADC trastuzumab-emtansine (T-DM1, Kadcyla®) drastically improved overall survival. However, T-DM1 is known to be a heterogeneous mixture of immunoconjugates, which compromises its therapeutic window. Moreover, despite the favorable efficacy profile of T-DM1 therapy in HER2-positive metastatic or locally advanced, unresectable breast cancer, acquired resistance is commonly observed during a continued treatment. There is consequently an urgent need to have access to new, more effective therapies. One of the different strategies that can be proposed to circumvent the T-DM1 resistance is the modification of the payload (cytotoxic agent), using a non-tubulin agent. In this project, we will develop original ADCs against HER2-positive mammary tumors, including novel payloads with non-classical mechanism of action. To obtain homogeneous ADCs, a chemical site-specific method, using patented heterobifunctional linkers will be used. This methodology allows the re-bridging of inter-chain disulfide bonds that were previously reduced in any native antibodies in order to build homogeneous and stable ADCs. The candidate will be in charge of payloads and linker-

payload entities synthesis. The applicant will also be responsible for the bioconjugation of the linker-payload entities to the mAb. Finally, the candidate will participate to the *in vitro* biological evaluation of the new immunoconjugates. ADCs characterizations and linker synthesis will be realized by different partners of this interdisciplinary scientific program.

Candidates profile:

The candidate must have a good knowledge of organic chemistry, and hold a PhD or an engineering degree in therapeutic or organic chemistry. An experience in medicinal chemistry will be much appreciated. Knowledge in biology, biochemistry and/or chemical biology will be welcome. An experience in cell culture will also be appreciated but not mandatory. The candidate must also be autonomous, demonstrate a high degree of motivation for working in an interdisciplinary project, and master organic synthesis and analytical techniques (especially HPLC).

Application procedure:

Caroline DENEVAULT-SABOURIN, MCU
UMR7292 GICC CNRS - Université de Tours
Equipe « Innovation Moléculaire et Thérapeutique »
UFR des Sciences Pharmaceutiques
31 avenue Monge, 37200 Tours
caroline.denevault@univ-tours.fr
Phone: 33 (0)2 47 36 72 31
Fax: 33 (0)2 47 36 72 29
Website: http://gicc.cnrs.univ-tours.fr

Additional information:

http://gicc.cnrs.univ-tours.fr
Keywords: cancer, therapeutic chemistry, organic chemistry, heterocyclic chemistry, bioconjugation, chemical biology.